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PHARMACOLOGY OF THE CORONARY CIRCULATION

by V. N. Kaverina

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FOREWORD

This book deals with one of the most important aspects of present-day medicine--pharmacological action on the coronary circulation. It is based on published material relating to the effects of pharmacological substances on blood circulation in the heart, information on the physiology of the blood circulation, the results of the author's investigations on the influence of adrenomimetic, cholinergic, and ganglion blocking agents, phenothiazine derivatives, analgesics, nitrites, and nitrates on the cardiac blood vessels, and the data on clinical tests of the new vasodilator chloracizin. It will be noted that there is no monograph in the Soviet or world literature specially concerned with the pharmacology of the coronary circulation.

The effect of pharmacological substances on blood circulation in the heart is considered by the author in terms of the peripheral and central regulation of the coronary blood flow. Since the blood supply of the heart depends on many factors, the author utilized different possibilities of pharmacological action on the coronary vessels, selecting for investigation substances differing in mechanism of action. The substances that influence the efferent innervation of the cardiac vessels include the adrenomimetics (epinephrine, norepinephrine), m-cholinomimetics (acetylcholine, carbocholine), m-cholinolytics (atropine), ganglion-blocking agents (nicotine, pentamine, hexamethonium, hexonium, mecamylamine). The substances that affect central regulation of the coronary circulation include analgesics (morphine, thecodine, promedol, phenadon), nitrites (sodium nitrite), and nitrates (nitroglycerin). In addition, a new class of pharmacological agents was tested--phenothiazine derivatives (chloracizin, mepazine, chlorpromazine).

In view of the complexity of physiological regulation of the coronary circulation, the author studied the effect of pharmacological agents on this process using a variety of methods. In evaluating the effects of drugs on the blood supply of the heart, considerable significance was attached to the volume rate of the coronary blood flow, tone of the cardiac vessels (from resistance to the blood flow), oxygen consumption of the heart, and cardiac function. The analysis is very logical and based on a high experimental level, using the most advanced techniques of present-day physiology.

The investigations were quite successful. Valuable data were obtained on the mechanism of action of the above-named agents on the coronary circulation. Specifically, the two-phase nature of the action of epinephrine and norepinephrine on the cardiac vessels was demonstrated. Acetylcholine and carbachol were found to be capable of dilating the coronary vessels but not of improving the cardiac blood supply owing to hypotonia. The effect of ganglion-blocking agents on blood circulation in the heart was shown to depend on the relationship between their influence on the tone of the coronary vessels and blood pressure.

The author demonstrated that the effect of analgesics on the cardiac blood supply is due not to their direct action on the coronary vessels but to their capacity to inhibit the reflexes of these vessels. By careful analysis of the effect of nitrites and nitrates on blood circulation in the heart, the author developed a new conception of the mechanism of action of these agents on the coronary vessels, i.e., their favorable effect on the cardiac blood supply is largely dependent on their capacity to inhibit the reflexes of the cardiac vessels.

All these findings provide new, more correct and precise ideas concerning the influence of many pharmacological agents on the cardiac blood supply. It is to be hoped that they will be the basis for a sounder utilization of these drugs in the treatment of diseases associated with impairment of the coronary circulation.

After studying the relationship between the chemical structure and pharmacological action of compounds of the phenothiazine series, the author proposed a new and highly effective drug--chloracizin. Clinical tests of this compound have shown it to be valuable in treating certain types of impairment of coronary circulation. Thus, these investigations have great practical value.

We anticipate that this book will find many readers among both pharmacologists and internists.

V. V. Zakusov, Member, USSR
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INTRODUCTION

Diseases associated with impairment of the coronary circulation are very common. Hence, the treatment of such diseases is a matter of considerable importance. It is now considered one of the main problems of clinical medicine. The basis for solving the problem is to enlarge our knowledge of the mechanisms of action of the drugs used to treat coronary insufficiency and to find new effective agents.

Owing to the complexity of physiological regulation of the coronary circulation, there are many difficulties of a procedural order in studying it experimentally. This was one of the reasons why ideas on the action of many pharmacological agents were derived until recently from the results of experiments involving the isolated heart. When applied to the intact organism, these ideas proved to be inexact and, at times, wrong. Some ideas on the effects of certain drugs were based on experiments involving the intact organism, but the data proved to be inexact due to the inadequacy of the method selected by the authors to determine the mechanism of action of a given substance.

Another reason for misconceptions of the effects of some drugs stemmed from insufficient knowledge and contradictory opinions expressed by various investigators on many aspects of the coronary circulation. Now, however, advances in experimental techniques have produced new facts bearing on the physiological regulation of the cardiac blood supply. This has given rise to the need to reexamine some matters concerned with the influence of pharmacological agents on the coronary circulation, relying on modern ideas concerning its physiological regulation and using adequate experimental techniques.

Most drugs have complex mechanisms of action owing to the intimate relationship between the processes regulating the cardiac blood supply. Elucidation of these mechanisms requires the use of various techniques, each of which must be suited to the particular aspect under study. This approach will result in a reappraisal of the action of several pharmacological agents on the coronary circulation. Moreover, we believe that the data in this book will be helpful in making more efficient use of these agents in the treatment of various forms of coronary insufficiency.

CURRENT STATUS OF THE PHARMACOLOGY OF THE CORONARY CIRCULATION

The problem can be considered from many aspects. The ways in which pharmacological agents may affect the cardiac blood supply vary with the conditions that determine it. Therefore, before discussing the pharmacology of the coronary circulation, we must discuss the physiological mechanisms that regulate the blood supply. The main criterion of the state of the blood supply is generally taken to be the volume rate of the coronary blood flow. This value, i.e., the volume of blood that passes through the cardiac vessels in a given unit of time, results from the interaction of several mechanical, biochemical and neurogenic factors responsible for the delicate and multifaceted regulation of the myocardial blood supply.

The volume rate of the blood flow in the cardiac vessels, as in the vessels of any other organ, is determined by the correlation between the energy moving the blood and the forces causing this energy to be lost. The movement of blood is determined by the potential energy of blood pressure. As the blood moves, this energy is expended on overcoming the resistance of the blood vessels to the flow of blood. It is obvious, therefore, that the volume rate of the blood flow Q in the vessels of any organ is proportional to arterial pressure (P) and is inversely proportional to the resistance (R) of the vessels of this organ.

$$Q = \frac{P}{R}$$

The peculiarities of blood circulation in the heart are due primarily to the fact that the coronary vessels are the vessels of the organ that supplies the energy required to move the entire mass of circulating blood. The cardiac blood supply obviously depends mostly on its own effectiveness as a generator of the energy of arterial pressure. The more efficiently the heart works, the stronger the stroke volume and, other conditions being equal, the arterial pressure and, consequently, the greater the blood flow is in the coronary vessels. However, increased ejection of blood by the heart does not necessarily result in an elevation of arterial pressure. If meanwhile the resistance of any of the peripheral vessels decreases (as happens, for example, during muscular exertion), arterial pressure need not rise and, in fact, it may fall, despite the increase in cardiac output. Obviously this situation should create disadvantageous conditions for the cardiac blood supply. But this does not occur under normal conditions because the body is capable of regulating the cardiac blood supply in another way--through the resistance of the cardiac vessels to the flow of blood. In fact, even with unchanged or lowered arterial pressure, the coronary blood flow may be increased by a reduction in the resistance of the cardiac vessels. The formula noted above, which shows the relationship between arterial pressure and resistance of the coronary vessels, is valid only for the most general statement of energy relations.

With an increase in the aortic pressure, the blood flow in the cardiac vessels naturally increases. However, it is important to note the mechanism by which this takes place. Judging by Osher's experiments (1953), which involved a study of the relationship between the coronary blood flow and magnitude of aortic pressure in the isolated dog heart, a slight increase in the aortic pressure sharply accelerates the rate of the coronary blood flow.

According to Poiseuille's law, the flow rate of a liquid in a system of rigid tubes increases in proportion to the pressure. If this law were applicable to the cardiac vessels, an increase in aortic pressure of a given number of times should cause an increase in the blood flow the same number of times. In point of fact, however, the coronary blood flow increases many more times than one would expect from Poiseuille's law. This happens because an increase in aortic pressure stretches the coronary vessels so that their lumen enlarges and resistance decreases proportionately. Thus, arterial pressure is not only a source of energy to move the blood, but a factor which owing to the capacity of the vascular wall to stretch determines the size of the lumen of the coronary vessels. Blood pressure should be regarded as one of the mechanical factors that regulates the resistance of the cardiac vessels.

The significance of another and equally important factor is likewise related to the capacity of the coronary vessels to change the lumen under the influence of mechanical forces. Due to the elastic properties of the vessels, the size of their lumen naturally varies with the direction in which the mechanical force may be operating. In the case just considered, this force (arterial pressure) acted within the vessels so that the difference between the pressures within the vessels and in the heart tissues (the so-called transmural pressure) grew. However, when the pressure in the myocardium increases as it contracts, the transmural pressure decreases. As a result, the lumen of the cardiac vessels decreases and their resistance to the blood flow increases proportionately. This peculiarity of function of the coronary vessels, which is caused by the cyclical nature of cardiac activity, has been the object of a great many investigations.

With the help of special methods, the sensitivity of which permits the detection of fluctuations in the coronary blood flow at different periods of the cardiac cycle (the "phase changes" in the blood flow), it was found that during a systole, the contraction phase, and at the start of the ejection phase the rate of the coronary blood flow decreases. A sharp increase in extravascular resistance in the left heart results even in a reverse flow of blood in the left coronary artery. Then the coronary flow gradually increases simultaneously with increased pressure in the aorta. During a diastole the rate of the coronary blood flow increases, reaching a maximum by the middle of the diastole and decreasing once more as it ends (Gregg, Green and Wiggers, 1935; Green, Gregg, and Wiggers, 1935; Johnson and Wiggers, 1937; Green and Gregg, 1940). Such is the pattern of changes in the blood flow in the cardiac vessels during the cardiac cycle. This, however, does not exhaust the factors that may mechanically bring about changes in the cardiac blood supply. The rate of cardiac contractions significantly influences the volume rate of the coronary blood flow. It was found that changes in the coronary blood flow following an increase in the rate of contractions are caused by a shortening of the diastole. For example, under the conditions of a heart-lung preparation with a high

frequency of cardiac contractions induced by electrical stimulation of the heart, the volume rate of the coronary blood flow may decrease (Anrep, 1936). On the other hand, during an asystole caused by stimulation of the vagus nerve, the blood flows more rapidly in the cardiac vessels (Gregg and Sabiston, 1956). However, a study of fluctuations in the coronary blood flow resulting from spontaneous changes in the cardiac rate showed the two processes to be related. An increase in the cardiac rate intensifies the coronary blood flow. This relationship may also be observed in a heart-lung preparation (Katz, Wise and Jochim, 1945a, b) and in experiments on the heart in situ (Eckenhoff, Hafkenschiel and Landmesser, 1947; Foltz, Page, Sheldon, Wong, Tuddenham and Weis, 1950).

Note, however, that the influence of changes in the cardiac rate on the coronary blood flow obviously cannot be regarded as mechanical. Laurent et al. (1956) and Alella et al. (Alella, Williams, Bolene-Williams and Katz, 1955; Alella, 1956) found that an increase in the volume rate of the coronary blood flow, which may follow an increase in the cardiac rate, results from changes that take place in the rate of myocardial metabolism. According to Alella, the parallelism of these processes persists only if there are no marked changes in cardiac function.

Thus far we have considered only the mechanical factors that affect the resistance of the vessels of the heart and, consequently, its blood supply. The conditions that determine the state of the cardiac blood supply are so closely interrelated that it would be quite artificial to separate them. We pointed out above that arterial pressure exerts a double influence on the cardiac vessels in that it both determines the energy of blood flow in these vessels and facilitates their mechanical distention. There is still another important mechanism for regulating the cardiac blood supply and the intensity of its manifestation varies with the level of systemic arterial pressure. An elevation of arterial pressure is known to increase the heart's load, resulting in changes in the metabolism of the myocardium. According to some investigators, changes in the cardiac output, the second component responsible for the intensity of cardiac function, do not markedly affect the blood supply. It was found in the intact organism that changes in cardiac output are not significantly reflected in the volume rate of the coronary blood flow, provided that meanwhile there are no important changes in the level of systemic arterial pressure. For example, Katz and coauthors (Katz, Katz and Williams, 1955) performed experiments on a heart preparation in situ under conditions that enabled them to control the influence of certain factors on the coronary blood flow by stabilizing one of them or by smoothing out their fluctuations. They discovered that when blood pressure is stabilized, a marked increase in cardiac output does not significantly intensify the volume rate of the coronary flow. It is interesting to note that if the blood pressure level remains high, changes in the coronary flow are more pronounced. If blood pressure is stabilized at a low level, even a sharp rise in cardiac output does not affect the flow rate in the coronary vessels (Anrep and Segall, 1926).

It is clear from the foregoing that changes in the coronary blood flow are determined by the energy expended by the heart in performing mechanical work, the intensity of which largely depends on the level of systemic arterial pressure. An increase in the heart's load intensifies myocardial metabolism, resulting in the establishment of a new level of blood supply.

The coronary vessels are known to be extremely sensitive to the oxygen content of arterial blood. In experiments on the heart in situ, it was found that a decrease in oxygen content of arterial blood, even though it does not reach the lower limits of the physiologically normal, increases the volume rate of the coronary blood flow (Rein, 1951; Alella, 1954). Several investigators demonstrated that the blood flow increases in the cardiac vessels with a decrease in oxygen content of arterial blood regardless of cyclical changes in cardiac activity, rate of heart beats, extracardiac innervation, or other factors (Green and Wegria, 1942; Wiggers, 1954; others). Thus, the level of the myocardial oxygen supply is obviously one of the major factors responsible for changes in the tone of the coronary vessels. There is a definite relationship between the volume rate of the coronary flow and the myocardial oxygen consumption of the myocardium (Spencer, Merrile, Powers and Bing, 1950; Foltz, Page, Sheldon, Wong, Tuddenham and Weis, 1950). An increase or decrease in myocardial oxygen consumption causes changes in the coronary blood flow in the same direction. The heart muscle consumes oxygen very rapidly. The venous blood of the coronary vessels under normal conditions contains only 20-30 percent oxyhemoglobin, which constitutes the "myocardial oxygen reserve." Under these conditions the oxygen requirement of the myocardium that is intensified by various factors naturally cannot be satisfied owing to the still greater decrease in oxygen content of the coronary blood. Therefore, the only possible mechanism for satisfying the myocardium's need of oxygen is obviously an increase in the volume rate of the coronary blood flow.

Some investigators (Foltz, Page, Sheldon, Wong, Tuddenham and Weis, 1950; Alella, Williams, Bolene-Williams and Katz, 1955) made a statistical analysis of the connection between changes in myocardial oxygen consumption and volume rate of the coronary blood flow, concluding that these processes are closely correlated. They deduced from their data that the level of myocardial oxygen consumption is the condition that determines the intensity of the corresponding changes in the coronary blood flow

Without denying the soundness of this view, Scott and Balourdas (1959) critically examined the analytical data used by these authors as confirmation of the functional relationship between changes in the coronary blood flow and rate of myocardial oxygen consumption. They showed that the correlation established is false because the volume rate of the coronary flow is taken into consideration when calculating the amount of oxygen utilized by the heart, i.e., there is a correlation between two parameters with a common element--the value of the volume rate of the coronary blood flow. This kind of statistical analysis clearly cannot serve as proof of a strict functional relationship between the magnitude of the volume rate of the coronary blood flow and the intensity of myocardial oxygen consumption. The data indicate that the correlation between myocardial oxygen consumption and volume rate of the coronary blood flow noted by many authors throws no light on the mechanism by which the correlation arises and is maintained at a given dynamic level. The commonest view is that the accumulation of metabolites in the myocardium is a signal for the volume rate of the coronary blood flow to increase.

In this connection the observations of Berne and coauthors (Berne, Blackmon and Gardner, 1957) are of interest. These investigators perfused the coronary vessels of a dog recipient with the blood of a dog donor, using for

this purpose a pump to keep the perfusion pressure constant. They found that when the perfusion pressure is at a high level, i.e., the myocardium is rapidly supplied with blood, a lowering of oxygen tension in the arterial blood flowing into the coronary vessels does not increase the volume rate of the coronary flow. These observations led the authors to conclude that a low level of oxygen tension in arterial blood cannot by itself cause the rate of the coronary blood flow to increase. The parameter that regulates the blood flow is evidently the rate of myocardial oxygen consumption. Thus, a factor in regulating the coronary blood flow is myocardial hypoxia and not a lowering of the oxygen content of the arterial blood.

However, this conclusion was not confirmed by Guz and coauthors (Guz, Kurland and Freedberg, 1960), who discovered that a decrease in the oxyhemoglobin concentration of the blood during perfusion of the isolated rabbit heart at a constant pressure causes the coronary blood flow to increase. At the same time there are no significant changes in the cardiac rate, pressure in the ventricles, or myocardial oxygen consumption. These authors believe, therefore, that a decrease in oxygen content of the arterial coronary blood is a signal for the volume rate of the blood flow to increase.

The prevalent opinions on the mechanism serving to link the processes responsible for changes in myocardial metabolism to the level of the cardiac blood supply are clearly contradictory. Further experimental study will be required before the problem is finally solved.

The data presented testify to the great importance of hemodynamic conditions, cyclical changes in cardiac activity, and, above all, the level of intensity of the myocardial metabolic processes in regulating the cardiac blood supply. However, the discussion of regulation of the coronary circulation would be incomplete without mention of nervous regulation of the tone of the coronary vessels.

The question of nervous regulation of the cardiac blood supply has long interested investigators. Although it stimulated a great many experimental studies, there still is no consensus on the nervous pathways through which this regulation is effected. The reason for this is to be found in the procedural difficulties involved in experimental work. Changes in the hemodynamics, cardiac activity, and intensity of myocardial metabolism observed after section or stimulation of the cardiac nerves make it difficult to identify the factors that directly influence the tone of the coronary vessels. The method of recording the volume rate of the coronary flow normally used to appraise the cardiac blood supply makes it impossible to distinguish changes in resistance of the vessels proper from hemodynamic and extravascular influences. Thus, the different authors have conflicting views on the subject.

The view with the most support is that vasoconstricting impulses are transmitted along the vagus nerve to the coronary vessels and that the sympathetic fibers act to dilate them (Morawitz and Zahn, 1912; Anrep and Segall, 1926; Rein, 1932; Gollwitzer-Meier and Kruger, 1935; Green, 1935; I. A. Baryshnikov, N. V. Bekauri and Ye. A. Moiseyev, 1949; others)

Other investigators, however, maintain that stimulation of the sympathetic nerves or injection of epinephrine or norepinephrine may constrict the coronary vessels (Katz, Linder, Weinstein, Abramson and Jochim, 1938; Katz and Jochim, 1953; Smith, 1950; Smith, Syverton and Coxe, 1951; Lu and Melville, 1951; Brose, Schaefer, Brendel and Gladewitz, 1953). This view is confirmed by some clinical observations of angina pectoris attacks being accompanied by a number of symptoms indicative of excitation of the sympathetic nervous system. Still others believe that, in general, nervous regulation of the coronary vessels does not play an important role in the myocardial blood supply and that there are virtually no direct vasomotor influences on the cardiac vessels (Shipley, Rotta, Gregg and Pritchard, 1941; Shipley and Gregg, 1945; Eckenhoff, Hafkenschiel, Landmesser and Harmel, 1947; Eckstein, Stroud, Dowling, Eckel and Pritchard, 1949; Eckstein, Stroud, Dowling and Pritchard, 1950; Okinaka et al., 1958). This conclusion was derived mainly from the fact that stimulation of the cardiac nerves intensifies the coronary blood flow due to intensified myocardial metabolism.

Many investigators are inclined to regard this secondary effect resulting from increase in the rate and force of heart contractions as the principal manifestation of the influence of the sympathetic nervous system on the level of the cardiac blood supply. For example, Shipley and Gregg (1945) concluded from their experiments with stimulation of the stellate ganglia that the cardiac nerves are not primary participants in the mechanism responsible for changes in the cardiac blood supply. Intensification of the contractions by stimulation of these nerves increases cardiac metabolism and results in dilatation of the coronary vessels. Thus, these authors believe, the role played by the cardiac sympathetic nerves consists of adapting the coronary blood flow to the intensity of the work performed by the heart.

The foregoing clearly illustrates in our opinion, the dissimilarity of experimental observations and contradictory judgments expressed by different authors on the part played by the nervous system in regulating the cardiac blood supply. However, in recent years new findings have been published which throw light on the innervation of the coronary vessels.

Before discussing them, we must note that the ideas concerning the vasoconstrictor effect of the vagus nerves on the coronary vessels arose mainly from two experimental phenomena: (1) vagotomy increases the volume rate of the coronary blood flow; (2) stimulation of the peripheral segment of the sectioned vagus nerve generally helps to reduce the blood flow in the coronary vessels.

Several investigators attempted to determine the extent to which these phenomena depend on the direct influence of vagus impulses on the coronary vessels. Most investigators compared changes in the rate and rhythm of the heart with changes in the volume rate of the coronary flow that followed stimulation of the vagus nerve. However, it is generally impossible to differentiate vascular from extravascular effects in this kind of a comparison (Sassa, 1923; Eckenhoff, Hafkenschiel and Landmesser, 1947; Winbury and Green, 1952). Z. T. Samoylova (1957) conjectured that vasomotor fibers form part of the vagus nerves. She observed that when arterial pressure was stabilized, stimulation of the vagus nerve induced independent changes in the coronary blood flow and cardiac rate. However, this conclusion was based on indirect evidence.

More convincing results were obtained by Schreiner and coauthors (1957) who used the method of inducing an artificially assigned rhythm in their experiments. They found that vagus stimulation with a stabilized cardiac rhythm has no effect on the volume rate of the coronary blood flow, pressure in the ventricles, or myocardial oxygen consumption. Denison and Green (1958), who investigated average and phasic blood flow in the coronary vessels with an electromagnetic flow meter, came to a similar conclusion. They failed to observe any significant changes in the average coronary blood flow after vagus stimulation. They noted only slight phasic changes caused by lengthening of the diastole.

Of interest here are the observations of Scott and Balourdas (1959a, 1960), who showed that under the conditions of a chronic atrioventricular block neither vagotomy nor atropine causes the volume rate of the coronary blood flow to increase because in doing so no changes take place in the rate of ventricular contractions. They concluded from their experiments that the vagus nerve has no direct effect on the blood flow in the coronary vessels.

Szentivanyi and Nagy (1959), who observed that vagus stimulation in a heart preparation in situ generally causes no changes in the coronary blood flow, are of the same opinion. The occasional decrease in outflow from the coronary vessels following vagus stimulation was not duplicated after removal of the stellate ganglia and injection of dibenamine. However, this effect was relieved by atropine, from which the authors inferred that the vagus nerves contain sympathetic fibers capable of being excited by a reduction of the blood flow in the cardiac vessels.

Thus, in summing up the results of studies by different investigators who used some new procedures, we conclude that the vagus nerves do not directly exert a tonic influence on the coronary vessels. The effects of increasing the coronary flow after transecting the vagus nerves and decreasing the flow by stimulating them, which were the basis for assuming that the vagus nerves have a tonic vasoconstrictor action, are due to extravascular influences. There is no ready explanation for the variety of effects observed after the administration of acetylcholine and stimulation of the vagus nerves. Of interest in this connection are the data obtained by Folkow et al. (Folkow, Haeger and Uvnas, 1948; Folkow, Frost and Uvnas, 1949), who stimulated the stellate ganglia in experiments with perfusion of the coronary vessels and found a substance with the biological properties of acetylcholine in the perfusate. They conjectured that the heart has cholinergic vasodilating fibers of sympathetic nature and that dilation of the coronary vessels by acetylcholine may be due to its influence on the transmission of excitation along these fibers.

Some new information is also available on participation of the sympathetic nerves in tonic influences on the coronary vessels. Szentivanyi et al. (Szentivanyi and Kiss, 1956, 1957; Szentivanyi and Nagy, 1959) in experiments on a heart preparation in situ using selective stimulation of different sympathetic fibers and employing the method of pharmacological analysis showed that two groups of sympathetic fibers proceed toward the heart. Some of them intercepted in the stellate ganglia send postganglionic fibers to the muscular nodes of the cardiac conduction system. These fibers influence the metabolitic function of the myocardium. When stimulated they may secondarily increase the coronary

blood flow as a result of intensified myocardial metabolism. The other group of sympathetic fibers is not intercepted in the stellate ganglia. Their preganglionic fibers terminate in the ganglia lying in the heart muscle while the postganglionic fibers transmit constricting and dilating impulses to the cardiac vessels. This last was found in experiments which showed that the effect of fiber stimulation which results in dilatation of the coronary vessels may be relieved by atropine, the vasoconstricting effect--by dihydroergotamine. The addition of hexamethonium to the perfusate prevents reactions of both types. Thus, according to Szentivanyi and coauthors, tonic innervation of the coronary vessels is effected by the sympathetic nerves. These findings along with the above-mentioned observations on the role of the vagus nerves in regulating the tone of the coronary vessels oblige us to reconsider the earlier ideas on nervous regulation of circulation in the heart. There is, however, reason to question Szentivanyi's assumption regarding the presence of sympathetic ganglia in the myocardium itself.

We have already stated that the variety of regulatory influences on the cardiac vessels makes it difficult to determine the direct tonic effect of nerve impulses on them. This situation lent support to the view that influences of this kind are virtually absent. The recent work of Branchfeld, Monroe and Gorlin (1960) endeavored to elucidate this matter. These investigators found that "pericoronary denervation" (surgical removal of the nerve elements from the surface of the blood vessels or applying novocaine to them) markedly increases the coronary blood flow and reduces the rate of oxygen extraction. These facts show that the cardiac vessels have a definite vasomotor tone. Denervation causes a loss of this tone, resulting in increased coronary blood flow and myocardial oxygen consumption.

The data that we presented on nervous regulation of coronary vascular tone clearly illustrate the complexity of the problem. However, on the basis of the literature we find it plausible to believe that the coronary vessels have a definite neurogenic tone, apparently effected by the sympathetic nervous system. The vagus nerves do not seem to take direct part in conducting nervous impulses to the cardiac vessels so that their influence on the coronary blood flow is secondary, the result of changes in cardiac activity. The secondary effects of the sympathetic nervous system, reflected in changes in the rate and force of heart contractions and in the intensity of myocardial metabolism, naturally have a marked influence on the cardiac blood supply too.

In discussing nervous regulation of the coronary circulation, we did not comment on the reflexes, which can play a major role in changing the tone of the coronary vessels, because a later chapter deals with this subject specifically.

It is evident from this brief survey of the physiology of the coronary circulation that the regulatory mechanisms are not only highly varied but closely related. Presumably the close relationship between these mechanisms conceals significant compensatory potentials which are revealed when the coronary circulation becomes impaired. Compensatory mechanisms of this kind can obviously be activated by pharmacological agents.

The use of pharmacological agents may result in effects of the opposite kind. We are referring to the overcoming of reactions that originate in the heart in pathological states and are capable of impairing its blood supply.

It follows from the foregoing that current ideas on the regulation of the coronary circulation and clinical observations on the symptoms of its impairment afford the possibility of using drugs to normalize the cardiac blood supply. They may bring about changes in the blood supply by acting on the coronary vessels themselves, i.e., by influencing either the muscular elements or the nervous regulation of their tone. There is no doubt that the coronary circulation can be affected by substances that alter the hemodynamics, cardiac activity, or myocardial metabolism.

The cardiac blood supply can be changed then by substances with various mechanisms of action. The diagram in figure 1 illustrates the possible mechanisms of action of pharmacological agents on the volume rate of the coronary blood flow, the principal indicator of the state of the cardiac blood supply.

The diagram provides only the most general idea of the mechanisms of action of the pharmacological agents capable of influencing the coronary circulation. Many substances naturally have a complex mechanism of action that simultaneously changes several factors on which the intensity of the cardiac blood supply depends. Also, owing to the technical difficulties involved in studying the coronary circulation, efforts have been mainly directed until recently toward elucidating the phenomena observed after the administration of a given agent. The ideas on the mechanisms underlying the action of an agent are frequently inaccurate. In fact, such information is generally lacking altogether. Hence our diagram largely reflects the broad, but still unrealized, possibilities inherent in using pharmacological agents to normalize the cardiac blood supply.

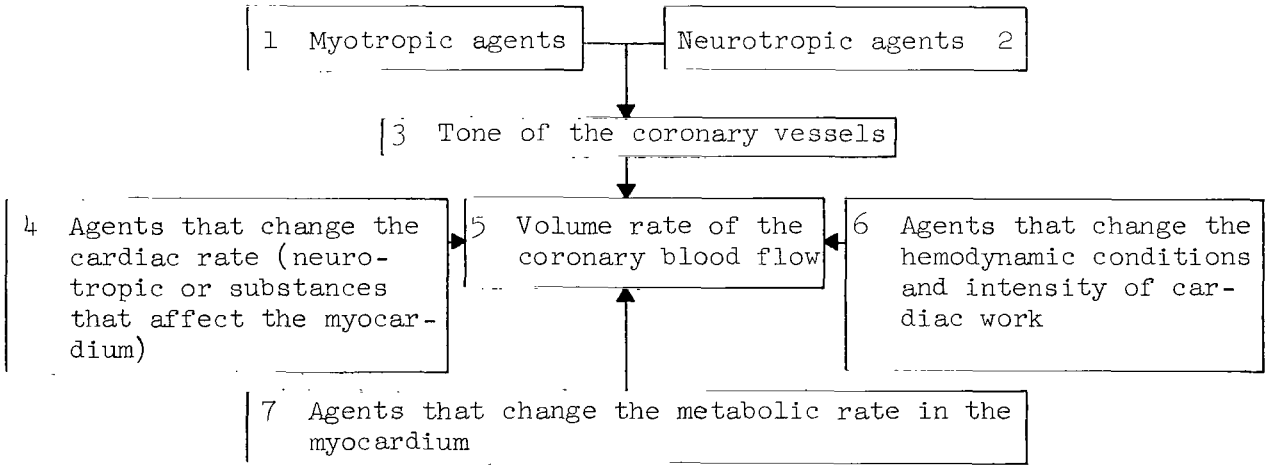


Figure 1. Diagram illustrating the possible mechanisms of pharmacological actions on the cardiac blood supply.

Before reviewing the literature, we should like to point out that the agents to which most attention has been directed to date are those affecting the cardiac vessels. The substances which influence other mechanisms regulating the myocardial blood supply have been less studied.

Most of the drugs that affect the cardiac vessels can be divided into two large groups, depending on their pharmacological action: (1) myotropic substances that act directly on the muscular elements of the vascular wall; (2) neurotropic substances that affect the nervous regulation of the cardiac vessels. The latter are further subdivided into those with central and peripheral action.

The agents with myotropic action are widely used in the treatment of coronary insufficiency. Perhaps the oldest and best known of these is papaverine. Over 50 years ago Macht (1915) found in experiments on the isolated heart that papaverine has a marked vasodilating action. His findings were subsequently confirmed by many investigators both in experiments on the isolated heart and under the conditions of a heart-lung preparation (Rössler, 1930; Linder and Katz, 1941; Elek and Katz, 1942). Experiments on intact animals using various experimental techniques revealed that papaverine is capable of increasing the volume rate of the coronary blood flow. It is also accompanied by a lowering of blood pressure and increase in cardiac rate (Essex, Wegria, Herrick and Mann, 1940; Linder and Katz, 1941; Eckenhoff and Hafkenschiel, 1947; Hanna and Shutt, 1953).

A detailed study of the effect of papaverine on the cardiac blood supply was made by I. Ye. Kisin (1958), who investigated the influence of this drug on the volume rate of the coronary blood flow, cardiac oxygen consumption and function. According to his data, papaverine causes a marked and prolonged (60-90 minutes) increase in the blood flow in the cardiac vessels. This effect develops under the conditions of hypotension and decreased heart action, although it is accompanied by an increase in oxygen consumption. Thus, papaverine does not entail a significant expenditure of energy (i.e., it does not add to the load on the heart), but it accelerates the rate of the coronary blood flow and increases oxygen consumption. Schlepper and Witzleb (1961) confirmed the capacity of papaverine to increase myocardial oxygen consumption.

To determine which of these processes is the primary one, I. Ye. Kisin (1960) performed special experiments in which the coronary vessels of the isolated heart in situ of a cat recipient were perfused with the blood of a cat donor. Under these conditions papaverine greatly increased cardiac oxygen consumption much more than it did the volume rate of the coronary flow. This fact is the basis for assuming that increased oxygen consumption due to papaverine is the primary process. To confirm this assumption, experiments were performed in which the coronary vessels were perfused by means of a pump operating with a constant volume of perfusion. Under these conditions papaverine could not accelerate the volume rate of the coronary flow, but it did increase the oxygen consumption of the myocardium. It follows from these experiments that the primary effect of papaverine is increased oxygen consumption by the heart. It is thus reasonable to believe that the mechanism of action of papaverine on the coronary circulation is related to the changes in myocardial metabolism that the drug induces. The fact that the volume rate of the coronary flow is increased

by papaverine along with a corresponding growth in oxygen consumption obscures the mechanism responsible for the clinical effectiveness of the drug.

It is interesting to note that the discrepancy between the distinct experimental capacity of papaverine to dilate the coronary vessels and its comparatively weak activity in the treatment of angina pectoris was detected by many investigators (Simon, Dolgin, Solway, Hirschmann and Katz, 1949; others). Nevertheless, several authors found that papaverine can improve the cardiac blood supply following experimental impairment. For example, Mokotoff and Katz (1945) observed a shrinkage of experimental infarcts in dogs under the influence of papaverine. It was also found that papaverine markedly increases the cardiac blood supply when acutely impaired by ligating one of the coronary arteries, as shown by the accelerated volume rate of the coronary flow, lengthening of the time between the origin of the impairment and development of arrhythmia, and survival rate of the animals (G. A. Markova, 1961). According to A. A. Myazdrikova (1960), papaverine likewise promotes the development of interarterial anastamoses in experimental myocardial infarction.

In conclusion, despite the great many experiments and many years' clinical experience in using papaverine, the delicate mechanism by which it improves the heart's blood supply is still obscure.

Compounds of the group of purine derivatives--theobromine, theophylline, diuretine, and euphylline--are also widely used for angina pectoris. The first to investigate these agents was N. P. Kravkov (1914), who found in experiments on the isolated heart that theobromine dilates the coronary vessels. Linder and Katz (1941) compared the effect of euphylline and papaverine on the vessels of the isolated heart. They found that under these conditions the effect of euphylline is much less pronounced than that of papaverine both in intensity and in duration.

Among the purine derivatives, euphylline has been the most studied in intact animals. According to the observations of a number of investigators who recorded the volume rate of the coronary blood flow by means of thermoelectric, diaphragm, and bubble flow meters in acute experiments on dogs, relatively small doses of euphylline cause a marked but brief (no more than 20 minutes) acceleration of the blood flow in the cardiac vessels. Its action is even more pronounced after intracoronary injection. But it does not significantly affect the blood pressure (Gilbert and Fenn, 1929; Le Roy and Speer, 1940; Boyer and Green, 1941; Eckenhoff and Hafkenschiel, 1947).

Essex et al. (Essex, Wegria, Herrick and Mann, 1940) investigated the effect of euphylline on the volume rate of the coronary flow in chronic experiments, using the thermoelectric method. They found that euphylline accelerates the rate, but the effect varies from experiment to experiment both in intensity and in duration. The above-mentioned investigations on the purine derivatives (chiefly euphylline) do not give a very precise idea of their mechanism of action on the cardiac blood supply. The most interesting works in this respect are those which investigated more broadly the influence of euphylline on the coronary circulation, i.e., not only the volume rate of the coronary flow but some other indices of the cardiac blood supply were recorded. For example,

Folz et al. (Foltz, Rubin, Steiger and Gazes, 1950) using the nitrous oxide method recorded fluctuations in the volume rate of the coronary blood flow simultaneously with changes in cardiac output and oxygen consumption. They found that euphylline somewhat intensifies the blood flow in the cardiac vessels while increasing the cardiac output and oxygen consumption. The authors note, however, that the results varied from experiment to experiment.

These data throw doubt on the beneficial effect of euphylline on impaired coronary circulation because the resultant increase in volume rate of the coronary blood flow develops under the conditions of intensified cardiac activity and thus compensates the energy expenditures of the myocardium.

I. Ye. Kisin (1958), who also investigated the effect of euphylline on the cardiac blood supply, oxygen consumption, and activity, obtained somewhat different results. He too found that the drug intensifies the blood flow in the cardiac vessels at the same time that it increases myocardial oxygen consumption. The latter does not seem to be due to the changes in cardiac activity induced by euphylline because these changes are insignificant and do not coincide with the acceleration of the coronary blood flow.

These observations, though interesting, likewise fail to clarify the mechanism responsible for the clinical effectiveness of euphylline because myocardial oxygen consumption under the influence of this drug, according to Kisin, exceeds the increase in volume rate of the coronary flow. Yet euphylline has been found to be effective both in experimental impairment of the coronary circulation and in the clinic by many investigators (Fowler, Harevitz and Smith, 1937; Gold, Travell, and Modell, 1937; Levy, Bruen and Williams, 1940; Leslie and Mulinos, 1942; Mokotoff and Katz, 1945; others).

Dibazol and khellin, myotropic agents, are also used in the treatment of coronary insufficiency. According to experimental data, the increase in volume rate of the coronary blood flow under the influence of dibazol is slight and transient (D. S. Paskov, 1948; I. Ye. Kisin, 1958). This was especially pronounced in experiments on intact animals. Since dibazol possesses hypotensive action, the slight increase in the coronary flow that immediately sets in after it is injected frequently gives way to a decrease. This phenomenon will not appear strange if we recall that after blood pressure is lowered, despite the dilatation of the coronary vessels caused by dibazol, the volume of the blood flowing through them in a given unit of time may diminish.

Thus, there seems to be little value in using dibazol to treat coronary insufficiency. Although the published reports on dibazol are few in number, they indicate that its therapeutic value is limited. But the impression one gets in studying the literature on khellin is quite different.

Despite the numerous studies dealing with the effect of khellin on the coronary circulation, the opinions of the investigators on the nature of its vasodilator action and clinical effectiveness are conflicting. Samaan (1931) was the first to study in detail the pharmacological properties of the pure crystalline preparation. He found that it is capable of relaxing the smooth muscles of the intestine, bronchi, and coronary vessels.

Later, the vasodilator properties of the drug, mainly with respect to the cardiac vessels, were thoroughly investigated by a number of authors (Anrep, Barsoum, Kenawy and Misrahy, 1946; Samaan, Hossein and Fahim, 1949; Anrep, Barsoum, Kenawy and Misrahy, 1947; Killam and Fellows, 1950a, b; Leusen and Essex, 1953; D. T. Kolesnikov, Ya. I. Khadzhay, et al., 1953; Ya. I. Khadzhay, 1957, M. A. Angarskaya, Ya. I. Khadzhay, et al., 1959). Khellin was found to accelerate the rate of the coronary blood flow both in experiments involving a heart-lung preparation and in intact animals. It is also capable of preventing spasms of the coronary vessels caused by the injection of pituitrin. It is variable in effect--the increase in volume rate of the coronary flow after intravenous injection is sometimes very indistinct or even absent (Farrand and Horvath, 1959).

It is interesting to note that in intact animals khellin accelerates the volume rate of the coronary flow without markedly lowering the blood pressure. This led some investigators to assume that the capacity of the drug to improve the circulation in the heart is not due solely to its myotropic action on the coronary vessels (Fellows, Killam, Toner, Dailey and Macko, 1950; Killam and Fellows, 1950; Wegria, 1951). The results of clinical trials of khellin in the treatment of coronary insufficiency are conflicting. Some investigators report that it prevents both the development of anginal pain and the appearance of EKG changes in patients when performing physical labor (Anrep, Barsoum, Kenawy and Misrahy, 1947; Roseman, Foshman, Kaplan, Levin and Katz, 1950; Ambrust and Levine, 1950). Other investigators, however, doubt that the drug is active, contending that its effect, when objectively analyzed, is little more than that of a placebo (Greiner, Gold, et al., 1950; Hultgren, Robertson and Stevens, 1952).

It is interesting to note that the chemical structure of khellin was the basis for synthesizing several compounds superior to it in potency of vasodilator action, specifically, the benzofuran derivatives synthesized by Beaudet and Henaux in 1959 (cited by Charlier, 1959). The most active of these compounds is ethyl-2(diiodo-3.5, 4 hydroxybenzoyl)-3 benzofuran, which has been given the name of amplivix. Charlier (1961) made a detailed pharmacological study of this drug. He found it to be a myotropic agent in its mechanism of coronary-dilator action. According to his earlier observations (1959), it has an affinity for the coronary vessels because much smaller doses are needed to achieve a given increase in the blood flow in the cardiac vessels than in the vessels of the extremities. A comparison of amplivix with some well known drugs showed it to be much more potent than most of them. For example, in in vitro experiments (on an isolated fibrillated heart) it proved to be 100 times more active than khellin, while in intact animals its effect on the coronary flow was 20 times greater than that of papaverine. In addition, the effect lasts for some time (2-3 hours). Amplivix should find wide use in the treatment of angina pectoris.

Until recently, the only substances known to have direct action on the smooth musculature of the cardiac vessels were the nitrites. But observations of late have shown that nitroglycerin has a weak constrictor effect on the cardiac vessels, and our own experience suggests that the early ideas on the mechanism of action of the nitrites on the cardiac blood supply should be reexamined.

As will be seen below, the direct coronary-dilator action of nitroglycerin does not seem to play a major role in the mechanism of action on the coronary circulation. We believe that the nitrites should be classified with the agents that affect the central regulation of coronary tone.

The drugs with direct vasodilator action also include some substances of plant origin capable of improving the cardiac blood supply. Experimental studies have shown that preparations isolated from plants belonging to the parsley family are particularly active in this respect--daucarine, pasternine, anetine and atamantine (Ya. I. Khadzhay, 1957; M. A. Angarskaya and Ya. I. Khadzhay, 1959; Ya. I. Khadzhay, P. I. Bezruk and V. F. Kuznetsova, 1960).

Thus far we have considered pharmacological agents with a relaxing action on smooth muscle of the coronary walls. A substance with the opposite type of action is pituitrin, which is capable of reducing the cardiac blood supply by constricting the coronary vessels. A reduction of the blood flow in the cardiac vessels under the influence of pituitrin has been observed in experiments on the isolated heart (Katz, Linder, Weinstein, Abramson and Jochim, 1938), heart-lung preparation (Bodo, 1928; Narayana, 1933), and in intact animals (Wegria, Essex, Herrick and Mann, 1940; Green, 1940; Green, Wegria and Boyer, 1942).

Since pituitrin is a vasoconstrictor, it generally causes hypertension, although it sometimes fails to reduce the volume rate of the coronary blood flow. On the other hand, due to mechanical action brought about by elevation of pressure in the aorta, the blood flow in the cardiac vessels may at times even increase. This is obviously caused by the absence of any adverse effect of pituitrin on the course of the experimental myocardial infarct.

Mintz and Kondo (1946) investigated the effect of pituitrin on experimental myocardial infarction in dogs. Their assumption that the process could be aggravated in opposition to the action of vasodilators studied at the same time was not borne out by the results. Measurement of the size of the infarct, which served as a test in the investigation, showed that pituitrin did not change it significantly. The authors conjecture that constriction of the coronary vessels caused by pituitrin is neutralized by its hypertensive effect. Yet, judging by EKG changes, pituitrin markedly impairs the coronary circulation. These changes are expressed electrocardiographically, as a rule, in the appearance of a negative coronary T wave and a lowering of the S-T segment below the isoelectric line. In some instances, however, the S-T segment is above the isoelectric line, forming a high dome-shaped T wave. Injection of large doses of pituitrin disturbs the cardiac rhythm (chiefly the extrasystole) apparently because of sharp impairment of the cardiac blood supply. The capacity of pituitrin to impair the coronary circulation under experimental conditions was used to create a model of coronary insufficiency (Gruber and Kountz, 1930; Goldenberg and Rothberger, 1931; Ruskin, 1947; Kordik, 1951; Linder, Loudon and Werner, 1953; S. I. Teplov, 1956). It was also found that by constricting the coronary vessels pituitrin at the same time slows the cardiac rate and reduces the cardiac output and oxygen consumption (Resnik and Geiling, 1925; Wakim, Denton and Essex, 1954).

Neurotropic agents affecting the cardiac vessels include those of central and peripheral action. Among the former are ethyl alcohol, analgesics and nitrites. Since a special section of our investigations dealt with the effect

of analgesics and nitrites on the cardiac blood supply, we shall confine our discussion here only to the influence of alcohol on the coronary circulation.

In 1906 Dixon studied the effect of alcohol on the vessels of the isolated cat heart. He found that relatively low concentrations (0.1-0.2 percent) may dilate the coronary vessels. Increasing the concentration to 1-2 percent encourages a two-phase effect, i.e., initial dilatation of the coronary vessels gives way to constriction. Sulzer later discovered (1924) that in a heart-lung preparation 0.1-0.2 percent alcohol always reduces drainage from the coronary vessels. But in experiments on intact animals alcohol was found to increase the volume rate of the coronary flow. Lasker, Scherrod and Killam (1955) investigated the effect of alcohol on the outflow of blood from the coronary sinus and inflow into the coronary vessels (recorded with a rotameter). Intravenous injection of a 10 percent solution in doses up to 500 mg/kg significantly accelerated the volume rate of inflow and outflow from the coronary vessels. The experiments also showed ethyl alcohol to be just as active as aminophylline and papaverine (administered in doses corresponding to therapeutic doses) when infused intravenously, but less active when injected intraarterially.

The more pronounced effect of alcohol on the cardiac blood supply in the intact organism, especially when injected intravenously (but not intraarterially) is due to its central action. This was the conclusion of Russek et al. (Russek, Naegele and Regan, 1950), who found that alcohol taken per os for chronic coronary insufficiency prevents anginal pain upon physical exertion. It is interesting to note that it is even stronger in this respect than nitroglycerin. However, the latter prevents EKG changes from taking place at this time. This effect is not characteristic of alcohol. On the basis of their observations, the authors concluded that the effectiveness of ethyl alcohol in angina pectoris is due mainly to its central action, which results in an elevation of the pain threshold.

The observations described above do not fully elucidate the mechanism responsible for the favorable effect of alcohol on the coronary circulation. We can only assume that its effectiveness in angina pectoris is a manifestation of its central action, as expressed in inhibition of vasomotor impulses to the cardiac vessels and in reduced intensity of pain.

The pharmacological agents that influence the peripheral (efferent) innervation of the cardiac vessels are quite numerous. They include adrenergic, cholinergic, and ganglion-blocking substances. Changes in the coronary circulation may be induced by drugs that stimulate or, contrariwise, inhibit the transmission of nervous excitation to the cardiac vessels. But this seemingly simple situation is, in fact, complicated by two circumstances: a great variety of factors that regulate the cardiac blood supply and the complexity of the mechanisms that differentiate the action of the many pharmacological agents. This fully applies, for example, to the phenothiazine derivatives which, judging by the experimental observations, influence the peripheral innervation of the cardiac vessels without, however, ruling out the participation of other mechanisms. Since a study of the pharmacological agents that affect the peripheral innervation of the coronary vessels was the object of our own investigations, a review of the literature and discussion of the matters concerning the mechanisms of

action of most of these compounds will be presented in the appropriate sections (Chapters 1, 2, 3 and 5 in Part I).

Here we wish merely to comment on the complex esters of diphenyl acetic acid which have been used in the treatment of coronary insufficiency, namely, spasmolytin, tiphen, aprophen and diprophen. These compounds are known to possess ganglion-blocking and spasmolytic properties (S. S. Liberman, 1950; M. D. Mashkovskiy and S. S. Liberman, 1950, 1957). They are capable of increasing the rate of the coronary blood flow while accelerating the cardiac rate and slightly lowering the level of systemic arterial pressure. Aprophen proved to be the most active of these substances (Z. T. Samoylova, 1958).

Among the drugs that influence the nervous regulation of the coronary vessels may be included novocain, which has been fairly widely used during the past 10 years in the treatment of angina pectoris (I. I. Sivkov, 1952; K. F. Vlasov, 1952; L. K. Korchinskaya-Dunayevskaya, 1953; A. S. Klimova, 1954; Z. M. Volynskiy, 1955, 1956; V. A. Val'dman, 1956; F. Ye. Ostapyuk, 1957; others).

Although there have been no precise experimental observations justifying the inclusion of novocain in this group, the favorable effect on angina pectoris of a retrosternal blockade as well as some observations on EKG improvement and inhibition of vascular reflexes in impaired coronary circulation (M. Yu. Ladinskaya, 1959) resulting from administration of the drug indicate that it influences the nervous regulation of the cardiac vessels.

There have been just a few superficial experiments dealing with the effect of novocain on the coronary circulation. It was found to dilate the coronary vessels in isolated cat and rabbit hearts (V. A. Babichev, 1953). But in experiments on intact animals this effect was not so pronounced. According to Wegria et al. (Wegria, Ward, Frank, Dreyfuss, Brown and Hutchinson, 1951), intravenous injection of 1-10 mg/kg of novocain first reduces the volume rate of the coronary flow and then increases it. The reduction of the blood flow is paralleled by a lowering of blood pressure. However, the blood pressure then returns to the original level, but the volume rate of the coronary flow remains high for several minutes. The latter observation led the authors to conjecture that novocain is capable of reducing the resistance of the coronary vessels.

Acceleration of the volume rate of the coronary flow under the influence of novocain in experiments on the heart in situ with stabilization of blood pressure was also observed by Nuki (1957). But Eckenhoff, Hafkenschiel, Foltz and Driver (1948), who studied the effect of subdural injection of novocain, came to the opposite conclusion. They found that novocain causes hypotension accompanied by a decrease in the coronary flow, myocardial oxygen consumption, and cardiac action and efficiency. Judging by our own observations, novocain has a variable effect on the volume rate of the coronary flow, depending on the initial conditions of the cardiac blood supply. With a low original volume rate of the coronary flow, novocain generally accelerates it. On the other hand, with a rapid cardiac blood supply, novocain may increase the blood flow in the cardiac vessels (N. V. Kaverina and I. Ye. Kisin, 1958).

Novocain is quite effective in experimental myocardial infarction. According to N. F. Ryzhkova (1956), the use of novocain in myocardial infarction that follows ligation of one of the coronary arteries or administration of massive doses of epinephrine greatly improves the animal's condition and also completely normalizes the EKG. It is evident from these observations that the effect of novocain varies with the experimental conditions apparently because it has a broad spectrum of pharmacological action. The dissimilarity of experimental observations is clearly responsible for the manifestation of different aspects of its action on the organism. Presumably, fairly accurate ideas concerning the effect on the coronary circulation of such a complex drug as novocain can come either from experiments providing for simultaneous recording of the several processes on which the state of the cardiac blood supply depends or from the use of special analytical methods of investigation.

As mentioned above, many pharmacological agents change the cardiac blood supply by influencing the different factors that participate in its regulation. The intensity of the blood flow in the coronary vessels may be changed chiefly by using substances that influence the rate and rhythm of cardiac contractions. For example, quinidine in large doses may cause a pronounced bradycardia and reduce the outflow from the coronary vessels (Bodo, 1928), whereas this effect is absent when administered in small doses (Kountz, 1932). Atropine (see p. 58) and pilocarpine have the opposite effect (Kountz, 1932). According to recent experimental data (Scott and Balourdas, 1960), these substances relieve the inhibiting effect of the vagus nerves on the heart and increase the cardiac rate, resulting in intensified myocardial metabolism and coronary blood flow (p. 6).

Since the level of metabolism in the heart is one of the major conditions that determine its blood supply, it is natural to assume that changes in the myocardial metabolic processes can ipso facto influence the coronary circulation. However, such a mechanism of action of pharmacological agents on blood circulation in the heart is still within the realm of conjecture for most of them at this stage in our knowledge. The reason is that information about the relationship between the effect of pharmacological agents on the coronary circulation and the changes that they induce in different elements of cardiac metabolism require special experimental conditions if such information is to be obtained within the same experiment. Study of these matters naturally encounters a multitude of technical difficulties (need for simultaneous recording of many indices, performing experiments under chronic conditions, etc.). The literature on the problem consists of scattered observations or conclusions of indirect nature based on a variety of comparisons. With these considerations in mind, we may include certain hormones and vitamins among the substances that influence the coronary circulation by altering myocardial metabolism.

The thyroid hormone is the most important of the various hormones that take part in regulating cardiac metabolism. According to the observations of several investigators (Raab, 1953; Brewster et al., 1954, 1956), the effect of this hormone on cardiac metabolism is due to its ability to intensify the action of the catechol amines (epinephrine and norepinephrine). Under the influence of thyroxin and in hyperthyroidism, functional impairment of the heart occurs in the form of tachycardia, more intense ventricular contractions, and increase in the stroke volume. The same changes also occur after the administration of epinephrine.

Changes in cardiac metabolism following the administration of thyroxin are reflected in increased oxygen consumption by the myocardium and decreased energy effectiveness of the oxidation processes (McDonald et al., 1935; Gemmil, 1952; Wollenberger, 1949; Rabbeno, 1949). Since there is a marked parallelism between the effect of thyroxin and that of the catechol amines on myocardial metabolism, it is reasonable to believe that thyroxin affects the metabolic processes by means of epinephrine and norepinephrine (Raab, 1953).

The possibility of such a mechanism existing is confirmed by investigations on the effect of thyroxin on the cardiac blood supply. Essex et al. (Essex, Herrick, Baldes and Mann, 1935) studied the rate of the coronary blood flow in chronic experiments on nonanesthetized dogs using the thermoelectric method. They found that intravenous injection of thyroxin (1 mg/kg) accelerated the blood flow in the cardiac vessels. The effect set in gradually and reached a peak 48 to 96 hours after injection. Interesting data were also obtained by Bing et al. (Bing, Hammond, Handelsman, Powers, Spencer, et al., 1949), who recorded several indices of the human cardiac blood supply. They found that the volume rate of the coronary flow, cardiac output, action of the left ventricle, and oxygen consumption by the myocardium are much greater in hyperthyroid patients than in healthy persons.

The data pertaining to the effect of insulin on the cardiac blood supply and conclusions on its mechanism of action are vague. For example, Soskin et al. (Soskin, Katz and Frisch, 1934) observed EKG changes indicative of a deterioration of the blood supply after the administration of insulin. In their opinion, insulin has a double effect on the heart--indirectly (through changes in blood sugar concentration) and directly. The conclusion as to the indirect influence is based on the fact that the EKG changes induced by insulin and hypoglycemia are similar. The conclusion as to the direct influence is based on the fact that these changes are not reversed when the hypoglycemia is corrected. Yet, as the observations of Elek and Katz (1942) showed, insulin dilates the vessels of the isolated fibrillated heart.

These authors concluded from their observations that the adverse effect of insulin on the EKG results not from its direct action on the cardiac vessels but from changes in the myocardium proper. However, Elek and Katz' observations suggesting that insulin dilates the coronary vessels were not confirmed by experiments in a heart-lung preparation (Bodo, 1927). On the contrary, the administration of large doses (10 units) of insulin usually decreases the volume rate of outflow of blood from the coronary vessels. Thus, on the basis of the literature, it is difficult to reach any conclusion as to the nature of the influence of insulin on the coronary circulation.

Although the treatment of angina pectoris with male sex hormones is widespread, their effect on the cardiac blood supply has been little studied experimentally. The ability of testicular extracts to dilate the blood vessels of the isolated heart has been known for a long time (N. A. Prozhanskiy, 1907; V. Ya. Danilevskiy, Ye. K. Prikhod'kova and Z. Ye. Shavinskaya, 1924; A. A. Likhachev and M. P. Nikolayev, 1920). However, the recent experiments of I. K. Kisin (1958) on the intact organism have shown that the effect of the androgens is irregular. Testerone propionate and methyl testosterone were found to accelerate the volume rate of the coronary blood flow in only 50 percent of the cases.

Thus, information concerning the effect of the androgenic hormones on the cardiac blood supply is ambiguous. Obviously these substances should not be investigated solely in acute experiments because their action, according to I. Ye. Kisin, is slow and long-lasting (1-1/2 to 2 hours). Observations on their action in acute experiments are further complicated by the fact that the substances are insoluble in water and are therefore unsuitable for intravenous administration.

The effect of vitamins on the metabolism and blood supply of the heart has been very little studied. A thiamin deficiency is known to alter the metabolic processes in the myocardium. According to the data of several authors, under these conditions the oxidation of pyruvic acid in the heart is disturbed and less glucose and lactic acid are extracted from the blood (Randles, Himwich, Homburger, Himwich and Albany, 1947; Hackel, Goodale and Kleinerman, 1953). Evidence of these changes is seen in cardiac dysfunction, reflected in the appearance of arrhythmia, increase in stroke volume of the heart, and edema. There are no references in the literature to the kind of changes induced in myocardial metabolism by further administration of thiamin.

According to B. A. Ovchinnikov (1959), thiamin contributes to systemic improvement of patients with angina pectoris. Intravenous injection of the vitamin reduces pain and normalizes the EKG changes indicative of impaired cardiac circulation. However, study of the effect of thiamin on the coronary circulation showed that it was slight in experiments both on the isolated heart (I. Ya. Matusevich, 1949) and in intact animals (I. Ye. Kisin, 1958). The volume rate of the coronary flow following the administration of 5 mg/kg of thiamin rose by a maximum of 20-40 percent over the original level.

The only vitamin to have aroused interest as an agent for treating angina pectoris is nicotinic acid (V. S. Nesterov, 1948; A. V. Vinogradov, 1950; K. L. Bumazhnaya and L. D. Grinshpun, 1950). It was used apparently for its vasodilator properties. Experiments dealing with the effect of the vitamin on the coronary circulation were performed mainly on the isolated heart, and relatively small amounts were found to dilate the coronary vessels (K. L. Bumazhnaya and L. D. Grinshpun, 1950). According to I. Ye. Ganelina (1947), its effect on the coronary vessels depends on the concentration. In a low concentration (1:100,100) it dilates the vessels of the isolated arrested heart. A higher concentration constricts them. I. Ye. Kisin (1958) investigated its action in the intact organism. He found that it has a two-phase effect on the volume rate of the outflow of blood from the coronary sinus. It intensifies the blood flow in the coronary vessels by 10-20 percent immediately after injection. The blood flow returns to the original level in 1-2 min, but 5 min later it usually starts to decrease, achieving 20-30 percent of the original value in 10-20 min. The most pronounced effect follows the administration of 5-10 mg/kg.

There is no information in the literature on the mechanism of action of nicotinic acid. It is difficult to determine from the data presented above whether its effects are simply a manifestation of direct myotropic action or the result of other conditions.

Since metabolitic factors play a major role in regulating the cardiac blood supply by maintaining the coronary flow at the level required to provide for the energy consumption of the heart, it is highly important to study the effect of the different products of tissue metabolism on the coronary circulation. Therefore, the interest of many investigators has naturally been drawn to the subject of the effect on the cardiac blood supply of energy-rich phosphorus compounds, products of carbohydrate metabolism, and electrolytes. The effect of nucleic acid derivatives on the blood flow in the coronary vessels was studied both in experiments on an isolated heart and in a heart-lung preparation.

In 1929 Drury and Szent-Györgyi investigated the effect of adenosine and adenosinemonophosphate on drainage from the coronary vessels in experiments involving a heart-lung preparation. They found that these compounds significantly increased the volume rate of the coronary flow. Similar data were obtained in experiments on the isolated heart (Zipf, 1930; Wedd, 1931). In intact animals, adenosine and adenosinemonophosphate accelerated the volume rate of the coronary flow without markedly affecting the level of systemic arterial pressure (Wedd and Drury, 1934; Greene, 1936). These findings were confirmed by Essex et al. (1940), who observed an increase in the coronary flow in chronic experiments with adenosine. It is interesting to note that an increase in coronary flow, similar in intensity and dynamics of development to the effect of nucleic acid derivatives, was observed by Eckstein et al. (Eckstein, Chambliss, Demming and Wells, 1950) after injecting substances obtained by mechanical destruction of erythrocytes.

Winbury et al. (Winbury, Papiersky, Hambourger and Hemmer, 1953) compared in more detail the activity of several compounds of the adenine-ATP series, adenosinemonophosphate (AMP) adenosinediphosphate (ADP), adenosinetriphosphate (ATP), adenine, and adenosine on the cardiac blood supply. In acute experiments on dogs, the authors injected the above substances in doses of 1-8 mg, using a rotameter to record the entry of blood into the left coronary artery. ATP was found to be the most active on the coronary vessels. If its activity is taken as 100 percent, that of ADP is 95, AMP--28, adenosine--25 percent. Adenine had no effect whatever on the blood flow in the cardiac vessels. Comparing the chemical structure of these compounds with their vasodilator action, the authors concluded that to manifest this effect requires the presence of a structure representing adenine-9-riboside. The greater activity of ATP and ADP, they assume, is due to the energy of the macroergic bonds. However, no definite conclusions can be drawn from their experiments.

Wolt and Berne (1956) investigated the effect of several chemicals (nucleic acid derivatives, purine and pyrimidine) on the coronary blood flow and oxygen consumption of the myocardium. ADP and ATP were the most active, AMP and adenosine less so, while adenine was completely inactive. Compounds capable of accelerating the volume rate of the coronary flow also resulted in increased myocardial oxygen consumption. Since the increase in blood flow was more pronounced than the oxygen consumption of the myocardium, the authors' conjecture that the influence of these compounds on the blood flow in the cardiac vessels results not from an intensification of the metabolic processes in the heart, but from the direct vasodilator effect. This view does not appear to take full cognizance of the nature of the effect of these compounds on the myocardial blood

supply. There are some data suggesting that the brief vasodilator effect caused by the action of these compounds on smooth muscle may be maintained by the subsequent and longer increase in blood flow caused by changes in the myocardial metabolic processes (Dubois-Ferriere, 1951).

Some products of intermediate carbohydrate metabolism have also been investigated. According to Forsman and Lindstein (1946), succinic acid is capable of constricting the vessels of the isolated heart and increasing the amplitude of its contractions. Citric and malonic acids likewise have vasoconstrictor action, but it develops with decreased amplitude of the cardiac contractions. Tripod et al. (1955) in experiments on the heart isolated by Langindorf's method investigated the effect on coronary blood flow and cardiac activity of a series of metabolites--the acid products of the intermediate metabolism of carbohydrates. They found that when used in large concentrations, lactic, succinic, fumaric, hydroxyacetic, citric, hydroxymalonic, and butyric acids constrict the coronary vessels and inhibit cardiac activity.

Only propionic acid has vasodilator action. Since the oxygen consumption of the heart is determined largely by the conversion of carbohydrates, study of the effect of different products of carbohydrate metabolism on the cardiac blood supply is of considerable interest. However, it is evident from the investigations mentioned above that the current information on the subject is quite limited and superficial.

Among the substances of tissue nature, histamine, serotonin, and angiotonin have been studied for their possible effect on the cardiac vessels. In experiments on an isolated fibrillated heart, Katz et al. (Katz, Linder, Weinstein, Abramson and Jochim, 1938) found that histamine can dilate the coronary vessels. According to Kountz et al. (Kountz, Pearson and Koenig, 1934), the reaction of the revived human heart to histamine is variable. These authors observed in a beating heart coronary dilatation, whereas in an arrested heart this effect appeared only when the heart was arrested by perfusion with a solution with a low pH. In a heart-lung preparation and in experiments on intact animals, histamine generally accelerated the blood flow in the cardiac vessels (Narayana, 1933; Wegria, Essex, Herrick and Mann, 1940). The effect of histamine is brief (no more than 3-4 min). Similar data were obtained by Essex and coauthors in chronic experiments on dogs (Essex, Wegria, Herrick and Mann, 1940). Histamine has also been found to prevent coronary spasms caused by pituitrin (Rössler, 1930).

The effect of histamine on the blood vessels varies with the species of experimental animal used. According to Gunn (1929), histamine intensifies the outflow of blood from the coronary vessels of the cat heart, but decreases it after perfusion of the rabbit heart vessels. The coronary vessels of the ox heart is also constricted by histamine (Cruickshank and Subba Rau, 1927). The mechanism of action on the coronary circulation has not been specifically investigated, but, judging by some observations, its direct action on smooth muscle of the coronary walls seems to be the dominant factor. One cannot rule out, however, the possible role of increased cardiac output and rate under the influence of histamine (Weiss, Robb and Ellis, 1932; Hanna et al., 1959).

Although different aspects of the pharmacological action of serotonin have been widely studied in recent years, the information available concerning its effect on the coronary circulation is very limited. In 1952 Reid noted an increased outflow of blood from the coronary vessels and a more rapid cardiac rate in the isolated heart following the introduction of 4-20 mg/kg of serotonin into the perfusion stream. Schofield and Walker later (1953) investigated its effect on blood flow in the heart vessels when perfused with a pump designed to maintain a constant pressure. They found that serotonin markedly dilated the coronary vessels.

Maxwell et al. (Maxwell, Castillo, Cliford, Crumpton and Rowe, 1959) made a more detailed study of serotonin. In experiments on dogs they recorded the coronary blood flow and cardiac output (by Fick's method) and calculated the oxygen consumption of the myocardium. The drug was injected intravenously at a constant rate of 20 mg/kg a minute. The result was a marked increase in volume rate of the coronary flow (79 percent above the original level). Meanwhile the oxygen content of the blood in the coronary sinus rose 3.3 percent by volume. At the same time, myocardial oxygen consumption grew. These effects were accompanied by a lowering of blood pressure and tachycardia. Since there were no significant changes in cardiac output, heart work under the influence of serotonin was not affected. The authors concluded that serotonin has a beneficial effect on the coronary circulation, for, while it increases the oxygen supply of the myocardium, it does not increase cardiac activity.

At the present time it is difficult to express a definite opinion about the mechanism of action of serotonin on the cardiac blood supply. But judging from the literature, it is reasonable to assume that its effect is related not only to direct action on the cardiac vessels. For example, the resultant tachycardia, increased myocardial oxygen consumption, and perhaps other still uninvestigated aspects of serotonin's action on the myocardium may play a definite role in its mechanism of influence on the coronary circulation.

Angiotonin (hypertensin, angiotensin) is known to be able to contract the smooth muscles of various organs and blood vessels. Biological tests of the activity of angiotonin on different objects showed the effect to vary in intensity. According to Gross and Turrian, who compared the effect of angiotonin on blood flow in the vessels of different organs, the reaction of the coronary vessels to injection of the preparation differs from that of other blood vessels. In the renal and mesenteric arteries, angiotonin slows the volume rate of the blood flow. But in the cardiac vessels it increases the flow. This effect is less pronounced than that of epinephrine if both preparations are used in doses that induce hypertension of the same degree. An increase in the coronary flow under the influence of angiotonin occurred only in experiments on intact animals. Investigators who observed the effect of angiotonin on isolated heart preparations noted that it generally caused the coronary vessels to constrict (Hill and Andrus, 1941; Elek and Katz, 1942). Only rarely is the effect absent or is dilatation of the cardiac vessels insignificant after administration of angiotonin. Lorber (1942) found that a decrease in outflow of blood from the vessels of the isolated cat or dog heart under the influence of angiotonin is accompanied by a decrease in the diastole, increase in myocardial oxygen consumption, and increased cardiac work and efficiency. The author concluded that constriction of the coronary vessels after the administration of angiotonin is due, in part, to increased extravascular resistance.

It is fair to conclude from the foregoing that the increase in blood flow in the coronary vessels observed in experiments on intact animals is due not to the direct effect of angiotonin on smooth muscle of the vascular walls but to hemodynamic changes brought about by elevated pressure in the aorta.

The role of electrolytes in myocardial contractions has by now been fully explored. There have been many experimental and clinical observations indicating that certain alterations in the electrolyte balance may result in characteristic changes in cardiac activity capable of being recorded electrocardiographically. Therefore, one cannot doubt the need of studying the changes that may take place in the cardiac blood supply when the electrolyte ratio is impaired.

There is, however, only fragmentary information on the subject in the literature. Katz and Linder (1938) investigated the effect on the coronary vessels of changes in the concentration of sodium, potassium, and calcium ions in defibrinated blood which they used for perfusion of the isolated fibrillated dog heart. They found that increasing the concentration 1.2-2.75 times (by adding NaCl) above normal causes the coronary vessels to dilate. If the calcium concentration is increased 1.3-2.5 times (by adding CaCl), dilatation is even more pronounced and it lasts from 3-15 min. The effect of potassium ions varies with the concentration. When the latter is 1.04-1.5 times above normal in the solution perfusing the heart, the coronary vessels dilate. If increased even more (1.55-1.66 times above normal) the dilatation gives way to constriction. Similar results were obtained by Driscol and Berne (1957) in experiments on intact animals with perfusion of the coronary vessels. The blood flow increased only as long as the K ion concentration did not exceed 12.1 meq/liter. Higher concentrations resulted in vasoconstriction.

Magnesium sulfate is also known to be capable of markedly accelerating the coronary blood flow (Elek and Katz, 1942). This was the basis for using it (parenteral injection) in the treatment of coronary disorders (A. N. Perlya, 1956; Agranat, 1958; others).

In summary, the information now available concerning the effect on the coronary circulation of various chemicals that take part in the metabolic processes of the heart is fragmentary and inaccurate. Moreover, they were investigated with methods that made it impossible to elucidate their mechanisms of action.

Thus far, we have described investigations in which the authors started mainly from theoretical considerations regarding the possible nature of the action of different substances on the cardiac blood supply. But there is a substantial amount of published material derived from clinical experience. For example, the wide use of cardiac glycosides--indispensable substances for treating cardiac insufficiency--required precise information on the kind of changes that these agents may bring about in the cardiac blood supply. This subject was investigated in a series of special studies undertaken because there were indications in the literature that the use of cardiac glycosides may exacerbate the symptoms of coronary insufficiency and cause anginal pain (Fenn and Gilbert, 1932; others). A variety of techniques were employed. In acute experiments on

dogs in which the outflow of blood from the coronary sinus was recorded, the injection of digitalis and strophanthin generally resulted in a slight decrease in the volume rate of the blood flow or in a two-phase effect--decrease in blood flow followed by a slight increase (Gilbert and Fenn, 1932; Stewart et al, 1938; Linder and Katz, 1941; Scherrod, 1952). In experiments in a heart-lung preparation, the initial decrease in coronary flow under the influence of digitalis or strophanthin did not always occur.

According to Ginsberg et al. (Ginsberg, Stoland and Siler, 1938), the effect of digitalis on the outflow of blood from the coronary vessels in experiments involving a heart-lung preparation was in most cases two-phase. Bodo (1927) observed under the same experimental conditions only a slight increase in the volume rate of the outflow from the cardiac vessels. He ascribed this effect to decreased resistance of the coronary vessels because suitable doses of the drugs under study failed to induce changes in the cardiac output or blood pressure. Other investigators who used the thermoelectric method in chronic experiments were, in general, unable to detect any changes in the volume rate of the coronary flow following the administration of therapeutic doses of the drugs (Essex, Herrick, Baldes and Mann, 1938; Essex, Herrick and Visscher, 1938). Dearing et al. (Dearing, Barnes and Essex, 1944) investigated the effect of digifolin, digalen, digitoxin, and lanatoside on the volume rate of the coronary flow in chronic experiments using therapeutic and nearly toxic doses. They found that the coronary flow slowed only after the administration of large doses (60 percent of the lethal). Since the decrease in flow was not correlated with changes in the cardiac rhythm and blood pressure, the authors considered it the result of direct vasoconstrictor action.

The absence of regular changes in the coronary flow after the administration of therapeutic doses of various glycosides was also noted by investigators who used the nitrous oxide method. For example, Page et al. (Page, Wendel, Sheldon and Foltz, 1950) found that 0.026 mg/kg of ouabain only intensified the cardiac output but had no effect whatever on the volume rate of the coronary flow, oxygen consumption of the heart, cardiac rate, or arterial pressure. A slightly larger dose of ouabain (0.037 mg/kg) raised the blood pressure, decreased the cardiac rate, and intensified total peripheral resistance. However, here too there were no changes in the coronary flow. Similar data were obtained in investigations of other cardiac glycosides--digitoxin, strophanthin, etc. (Takayanagi, 1957).

Several investigations focused on the effect of cardiac glycosides on the coronary circulation in healthy and sick human beings. Bing et al. (1950) recorded the coronary blood flow (NO_2 method), cardiac output and oxygen content of venous coronary blood. They found that in healthy persons strophanthin reduced the cardiac output, actions, and efficiency while the coronary blood flow, arterial pressure, and cardiac oxygen consumption remained unchanged. Even in cardiac insufficiency, strophanthin did not affect the coronary flow, although it increased the action and efficiency of the heart. Interesting data were obtained by Ye. A. Veselov (1960), who studied the effect of strophanthin on the volume rate of the coronary flow and cardiac oxygen consumption. She observed that therapeutic doses of the drug had no significant effect on the volume rate of the coronary flow or cardiac oxygen consumption in healthy experimental animals.

In experimental myocarditis, the coronary flow and cardiac oxygen consumption increased somewhat when strophanthin was administered in relatively small doses (10 μg/kg). If the dose was raised to 20 μg/kg, the reaction of the coronary flow changed, i.e., it was considerably reduced. A slowing of the rate of coronary flow is paralleled by a decrease in cardiac oxygen consumption, resulting in bradycardia, which does not happen in normal animals receiving a similar dose of strophanthin. These effects do not appear if the vagus nerves are first divided. The investigations of V. V. Zakusov, Ye. A. Spalva and O. V. Ul'yanova (1957) showed that in experimental myocarditis strophanthin facilitates the transmission of excitation from the vagus nerves to the heart. These observations support the assumption that a decrease in coronary flow and cardiac consumption under the influence of strophanthin in experimental myocarditis may be caused by the facilitation of transmission of excitation from the vagus nerves to the myocardium. The resultant bradycardia, change in cardiac function, and metabolic rate can naturally affect the volume rate of the coronary blood flow.

The information available in the literature indicates that the cardiac glycosides change the blood supply conditions in the pathological heart, although they do not exert any marked influence on circulation in the healthy heart. Practical implications could presumably be drawn from a more detailed study of the effect of cardiac glycosides on the coronary circulation under different pathological conditions of the myocardium.

We are abstaining here from a detailed review of the literature dealing with the effect of cardiac glycosides on myocardial metabolism, referring those interested to the comprehensive article of Ye. Rotlin and M. Teshler (1959) on the subject. Such data, extremely important for understanding the therapeutic action of the cardiac glycosides on the contractility of the failing heart, cannot at present be readily compared with the data relating to their effect on the myocardial blood supply. No one has specifically investigated them for this purpose. Only a few studies include data obtained from a simultaneous recording of the blood flow in the cardiac vessels and oxygen content of the venous coronary blood (Page et al. 1950, Ye. A. Veselova, 1960). However, one cannot draw from these studies any definite conclusions concerning changes in the cardiac blood supply in relation to changes in myocardial oxygen consumption induced by these agents.

Another group of pharmacological agents the study of which was stimulated by clinical experience includes such stimulants of cardiovascular activity as camphor, cardiazol, and nikethamide. Very little is known about the effect of camphor on the coronary circulation. In experiments on the isolated heart and in a heart-lung preparation, camphor slightly accelerated the blood flow in the cardiac vessels (Bodo, 1928; Kountz, 1932). According to A. S. Saratikov, T. F. Marina and L. A. Usov (1960), camphor reduces the intensity of the EKG changes in cats caused by intravenous injection of pituitrin. No one has specifically studied the question of whether the increase in cardiac blood supply caused by camphor is a manifestation of its direct action on the coronary vessels or the result of extravascular factors. But since camphor is known to intensify the influence of the symphathetic nerves on the heart, it is fair to assume that the increase it brings about in the myocardial blood supply is caused not only by dilatation of the coronary vessels but by the action of extravascular factors.

The effect of cardiazol and nikethamide on the coronary circulation was the object of a great many investigations in which a variety of techniques was used. The results were largely the same. Nikethamide generally accelerated the volume rate of the coronary blood flow. The effect of cardiazol was slight.

The potency of nikethamide varied with the dose used and method of administration. In experiments on isolated fibrillated dog heart, an intensified outflow of blood from the coronary vessels followed the administration of cardiazol (Linder and Katz, 1941; Camp, 1928) and nikethamide (Elek and Katz, 1942). According to Leyko (1930), an increase in the outflow from the coronary vessels occurred in experiments with a heart-lung preparation after nikethamide was used in a 1:50,000 concentration. At the same time the ventricles enlarged. Cardiazol proved ineffective in this author's experiments.

In intact animals, nikethamide likewise intensified the volume rate of the coronary flow. Its action was much less pronounced. According to Greene (1936), intensified coronary blood flow under the influence of nikethamine occurs regardless of any changes in the level of systemic arterial pressure that may take place at this time. For example, the injection of large doses of nikethamide (of the order of 60 mg/kg) distinctly accelerated the blood flow in the cardiac vessels, despite the marked lowering of blood pressure. Similar results were obtained by Wegria et al., who studied the effect of this drug on the coronary circulation in chronic experiments on dogs using the thermoelectric method (Wegria, Essex, Herrick and Mann, 1940; Essex, Wegria, Herrick and Mann, 1940). Stoland and Ginsburg (1937) compared the effectiveness of cardiazol and nikethamide. They found in a heart-lung preparation and in experiments on the dog heart in situ that nikethamide intensified the volume rate of the coronary blood flow much more than did cardiazol. For example, in low doses (1 ml of 25 percent solution) nikethamide had a marked vasoconstrictor effect, whereas large, almost toxic doses of cardiazol were required to obtain a similar effect. Moreover, the action of cardiazol was brief (only 2-4 min).

Eckenhoff and Hafkenschiel (1947) made a more detailed study of nikethamide. They found that in a 5 mg dose injected directly into a coronary artery it intensified the volume rate of the coronary flow (recorded with a bubble flow meter), cardiac rate, and oxygen consumption. The effect was even more pronounced when a large dose (70 mg/kg) was injected intravenously. It was followed by a sharp increase in the coronary flow, cardiac rate, output, and oxygen consumption, but blood pressure dropped. As for cardiac work, it was found to increase somewhat, but the mechanical efficiency of the left heart decreased. Foltz and Elwood (1948) obtained similar results in their experiments.

In comparing the results of experiments by different investigators on isolated heart preparations and in intact animals, one gets the impression that the increase in cardiac blood supply under the influence of nikethamide is due not only to its vasoconstrictor action but to secondary metabolitic influences caused by an increase in the activity of the heart and rate of contractions.

In view of the wide use of sodium salicylate in the treatment of several cardiovascular diseases, it is worth mentioning the interesting observations of I. Ye. Kisin (1960), who discovered that 100 mg/kg doses of the drug infused

intravenously caused a transient but pronounced increase in the volume rate of the coronary flow and cardiac oxygen consumption.

Among the new pharmacological agents meriting the consideration of internists for treating angina pectoris are the monoaminoxidase inhibitors, specifically iproniazid (marsilid). It is interesting to note that the clinical use of this drug for angina pectoris preceded its experimental study. In 1958 Ceserman (1958) used it to treat psychopaths and found that it alleviated the symptoms of coronary insufficiency. These observations led to its use in the treatment of angina pectoris.

Experimental study of iproniazid showed that it has a direct vasoconstrictor action. But this action, judging by the results of experiments on the isolated heart, is weak and it occurs only when massive doses are used (Charlier, 1961). In intact animals the effect is somewhat stronger owing to its ability to increase extravascular resistance (Mendez, Aceves and Pulido, 1959). Iproniazid is capable of preventing coronary spasms caused by pituitrin and of relieving ventricular fibrillation caused by occlusion or ligation of a coronary artery in dogs (Fresia, Genovese and Morati, 1958; Pletscher and Pellmon, 1958; Regelson, Hoffmeister and Wilkens, 1959).

At present we have no direct experimental data that justify relating the properties of iproniazid as a monoaminoxidase inhibitor to its ability to improve the cardiac blood supply. Furthermore, it is difficult to evaluate the mechanism responsible for the beneficial effect in angina pectoris because of its broad spectrum of pharmacological action. Some authors (Gossio, 1958) link it to the drug's analgesic properties. Others (Mendez, 1959) believe that it results from the influence exerted by the products of iproniazid decomposition in the body.

In recent years anticoagulants--heparin, dicoumarin, and neodicoumarin--have been widely used in the treatment of myocardial infarcts and angina pectoris. The rationale for such use was the observations of several investigators who convincingly demonstrated that these drugs are capable of preventing the development of experimental thrombi in cardiac blood vessels (Solandt and Best, 1938; Solandt, Nassim and Best, 1939; others). The effect of coagulants on the cardiac blood supply has received very little experimental study. Gilbert and Nalefski (1949) investigated the effect of heparin and dicoumarin on the volume rate of blood drainage from the coronary sinus in dogs. They found that heparin intensified the blood flow in the cardiac vessels, although blood pressure and the cardiac rate did not change. It is interesting to note that, according to these authors, only the sodium salt of heparin is capable of intensifying the coronary blood flow. If heparin is used in the form of a barium salt, the blood flow is not intensified. The authors ascribe this phenomenon to the antagonistic effect of the barium ions on cardiac smooth muscle. In their opinion, the presence of barium ions overcomes the vasodilator effect of heparin.

Dicoumarin too intensifies the coronary flow, as shown in experiments on intact animals and on the beating isolated heart when perfused under a constant pressure.

K. M. Lakin (1960) studied the effect of neodicoumarin in acute experiments on cats with recording of the outflow of blood from the coronary sinus. He found that the drug intensified the coronary flow under normal conditions and, especially, in the case of pituitrin spasm of the coronary vessels. The author does not correlate the observed effect with dicoumarin's anticoagulant action because the latter set in after the blood flow accelerated in the cardiac vessels.

Our review of the literature reflects in the main the current ideas on the nature of the influence exerted by various pharmacological agents on the coronary circulation. We wish to stress once more that the agents which affect nervous regulation of coronary vascular tone (adreno- and cholinomimetic, ganglion-blocking, analgesics, nitrites and nitrates) are of great interest. Because their effect on the coronary circulation was the object of our own research, the pertinent literature will be cited in the appropriate chapters.

We presented a diagram illustrating the possible ways in which pharmacological agents may affect the cardiac blood supply. A comparison of the potentialities revealed by the diverse methods of regulating this blood supply with the extent to which they have been realized shows how limited our knowledge is on the mechanisms of action of the drugs. Therefore, it is reasonable to assume that a careful study of the mechanisms of action of certain drugs in the light of modern ideas on the physiology of blood circulation in the heart and the search for new effective pharmacological agents will substantially enlarge the arsenal of drugs available to practising physicians for the treatment of coronary disorders.

PRINCIPLES UNDERLYING THE METHODS USED IN STUDYING THE CORONARY CIRCULATION

Study of the coronary circulation is known to be one of the most difficult tasks from the technical standpoint, chiefly because of the complex and varied factors involved in regulation of the myocardial blood supply. We have already stated that the main criterion for judging the intensity of the blood supply is the volume rate of the coronary flow, which is largely regulated by mechanical, biochemical, and nervous factors. Thus, to study impairment of the coronary circulation requires the employment of several methods in order to gain as complete an idea as possible of the complex processes at work. It is just as important, however, to analyze the individual factors that greatly influence the myocardial blood supply. This approach requires the use of special analytical methods of investigation.

When investigating the effects of pharmacological agents, one must also take into account the action of each as well as the changes in the organism following their administration. Therefore, it is extremely important to select the methods most appropriate to the aspect of the problem under study.

The major criteria for judging the state of the coronary circulation are: (1) volume rate of the coronary blood flow; (2) resistance of the cardiac vessels to the blood flow; (3) oxygen consumption of the myocardium; (4) cardiac activity. The importance of each criterion varies with the specific purpose of the investigation.

Before discussing the methods, it might be well to review briefly the anatomical structure of the cardiovascular system. Blood is supplied to the heart by two main arteries--the right and left coronary arteries. The left coronary artery is divided into two branches: left descending and left reflex. It has been observed that the total amount of blood entering the dog heart ranges from 70 to 140 ml/min per 100 g of weight of myocardium. In doing so, 85 percent of the blood passes through the left coronary artery (Eckenhoff et al., 1948; Foltz, Page, Sheldon, et al., 1950; Gregg, 1950; Alella, Williams, Bolene-Williams and Katz, 1955). The arteries of the heart have less developed interarterial anastomoses than do the arteries of the other organs. This explains why obstruction of a large branch of one of the coronary arteries always results in a prolonged slowing of the blood flow below the obstruction site in the region supplied by this artery. According to Blumgart (1942), after ligation of the left descending coronary artery in dogs, the blood flow in the region distal to the ligation remains at a very low level for several hours. However, judging from experimental observations and pathoanatomical investigations, an insufficient myocardial blood supply creates conditions favorable to intensified development of collateral vessels.

The venous system of the myocardium is divided into superficial and deep-lying vessels. The former consist of the large coronary and anterior cardiac veins. The large coronary vein collects blood from the left ventricle and terminates in the coronary sinus, which opens onto the posterior surface of the right auricle. The coronary sinus drains 64-83 percent of the blood supplied to the heart through the left coronary artery. When the left coronary artery is compressed, the outflow of blood from the coronary sinus decreases sharply (93-95 percent below the original level). On the other hand, compression of the right coronary artery has virtually no effect on the outflow of blood from the coronary sinus (Gregg and Shipley, 1947). The anterior cardiac veins collect blood from the right heart and open onto the anterior surface of the right auricle (Gregg, Shipley and Bidder, 1943).

The deep venous system of the heart consists of a mass of Thebesian vessels which connect the distal ends of the capillaries and coronary veins with the heart cavities. It has been observed that the Thebesian vessels play a role in the drainage of blood from the right ventricle (Lendrum, Kondo and Katz, 1945). These findings have been criticized, however, because the experiments of these authors were performed on an arrested heart perfused with a nutrient solution and not with blood. Such experimental conditions make it impossible to evaluate the function of the Thebesian vessels (Gregg, 1950).

Taking up the various methods of studying the coronary circulation, we should like to begin by noting that the volume rate of blood flow in the cardiac vessels can be determined by recording the rate of inflow into one of the coronary arteries or outflow from the veins. The many techniques used to record the coronary flow are described in several surveys (Gregg, 1950; Wegria, 1951; N. V. Kaverina and I. Ye. Kisin, 1960).

In this investigation we used the method of recording the outflow of blood from the coronary sinus to determine the volume rate of the coronary flow. The above-cited data on the anatomical structure of the cardiac venous system show that the coronary sinus is the basis of the venous drainage of the heart. This makes it possible to use the rate of blood outflow from the coronary sinus as a criterion of the state of the cardiac blood supply.

The first to record blood drainage from the coronary sinus of dogs were Morawitz and Zahn (1912), who proposed a special cannula for this purpose. We tested this method in experiments on cats, inserting a polyethylene tube into the cavity of the coronary sinus. The principle involved in measuring the amount of blood flowing out of the coronary sinus of cats is as follows. In an acute experiment, the thorax of anesthetized cats given artificial respiration is opened up at the 5th-6th left intercostal space, followed by removal of 1-1/2 to 2 cm long portions of the 5th and 6th ribs and dissection of the pericardium. A purse-string suture is applied to the right auricle of the heart. An incision is made in the center of the portion of the auricle bounded by the suture and through it is inserted a polyethylene catheter filled with heparin solution. After the suture is tightened, the catheter is drawn from the auricle into the orifice of the coronary sinus. At the same time heparin (1000-1500 U/kg) is injected into the animal intravenously.

The diagram of the apparatus for measuring the volume rate of blood drainage from the coronary sinus is shown in figure 2. The free end of the catheter (1) is connected to a tee (4) through which the blood travels in a rubber tube (2) to the jugular vein (fig. 2c). The tee (4) is also connected by a rubber tube to a vertical glass tube (5). If pinchcock (6) is opened for a while and pinchcock (7) closed (fig. 2a), the blood starts to flow into the measuring tube (5). A freely moving float is connected to a light recording lever which traces on a kymograph the rising level of blood in tube (5) at a rate proportional to the volume rate of blood drainage from the coronary sinus. By knowing the time the pinchcocks are closed and the diameter of the measuring tube and then measuring from the tracing on the kymogram the height to which the lever has risen, it is possible to convert the corresponding figures into the minute volume of blood flow in the coronary sinus. The blood after entering measuring tube (5) passes through outlet (3) and returns to the venous system of the animal (fig. 2b). Blood pressure in the carotid artery is recorded with a mercury manometer at the same time that the volume rate of the coronary flow is measured, while the amplitude of cardiac contractions is determined with a myocardiograph and pneumatic transmission.

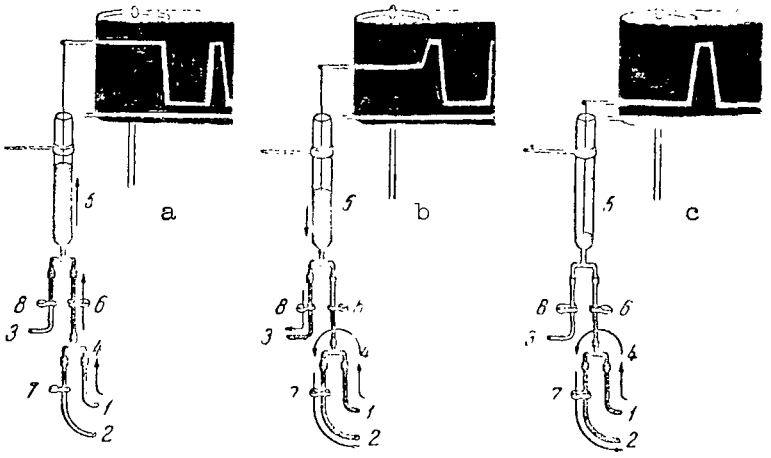


Figure 2. Diagram of apparatus for recording the drainage of blood from the coronary sinus of a cat.
a--Period of measurement of drainage. Blood from the coronary sinus flows through rubber tube (1) into measuring tube (5). Pinchcock (6) is open, pinchcocks (7) and (8) are closed. b--Flow of blood from measuring tube (5) through rubber tube (3). Pinchcocks (7) and (8) are open, pinchcock (6) is closed. Blood from the coronary sinus travels from the coronary sinus through tubes (1) and (2) and tee (4) into the cat's jugular vein. c--Period between measurements of drainage. Blood from the coronary sinus travels through rubber tubes (1) and (2) and tee (4) into the cat's jugular vein. Pinchcock (7) is open, pinchcocks (6) and (8) are closed.

One experimental variation is to record the volume rate of the blood flow in the cardiac vessel during a spasm induced by the injection of pituitrin. The use of this model makes it possible to trace the effect of pharmacological agents after impairment of the cardiac blood supply. Owing to the hypertensive effect of pituitrin, it is not always possible to record any decrease in the volume rate of the blood flow because elevated aortic pressure promotes compensation of the vasoconstrictor effect of pituitrin on the coronary vessels. In some of the experiments (50-60 percent), the elevation of blood pressure following intravenous injection of 1-2 U/kg of pituitrin caused the volume rate of the coronary blood flow to diminish. This occurred 1 to 2-1/2 min after injection and it lasted 15-20 min. Under ordinary circumstances, the amount of blood draining from the coronary sinus of a cat's heart ranges from 5-15 ml/min. When pituitrin is injected in the above-mentioned doses, the volume rate of blood drainage from the coronary sinus drops 40-50 percent below the original level, an indication of constriction of the coronary vessels. If pharmacological agents are administered after a coronary spasm, their effectiveness can be judged from the intensity of their action and from the period of time required to relieve the constriction of the vessels.

The prophylactic action of drugs against spasms of the coronary vessels induced by pituitrin can also be studied in chronic experiments on cats. The sharp spasm following the injection of pituitrin can be recorded electrocardiographically in the form of changes characteristic of impaired coronary circulation (Gruber and Kountz, 1930; Ruskin, 1947; Linder, Loudon and Werner, 1953; S. I. Teplov, 1956; others). In experiments on cats injected with pituitrin (2 U/kg), three types of EKG changes can be observed. The most typical is the formation of a negative coronary T wave and lowering of the S-T interval below the isoelectric line. In other cases, however, the S-T interval is below the isoelectric line, forming a high, dome-shaped T wave. The third type of EKG changes is marked by a disturbance of the rhythm, generally with the occurrence of an extrasystole, which is apparently the result of sharp impairment of the cardiac blood supply. These EKG changes persist for several hours, but they are most pronounced during the first 20-30 min after pituitrin is injected. A detailed description of these experiments is given in the section dealing with the effect of phenothiazine derivatives on the cardiac blood supply.

It will be noted that EKG recordings can be used only as a supplementary method for studying pharmacological agents experimentally because EKG changes do not always parallel changes in the rate of blood flow in the cardiac vessels.

In some cases the volume rate of the coronary blood flow, which is a composite index of the interaction of many factors, is also likely to be an insufficiently accurate criterion for judging the mechanism of action of pharmacological agents on the coronary circulation. This is primarily due to the fact that it is not possible to evaluate the tone of the cardiac vessels from a recording of the blood flow therein or, more precisely, from their resistance to the flow of blood.

The resistance of blood vessels in any organ, including the heart, is influenced by three factors to the extent that it is determined by smooth muscle: (1) arterial pressure, (2) humoral agents, and (3) nerve impulses. Therefore,

if in an experiment the condition of the blood vessels proper and level of arterial pressure change at the same time, the flow of blood in the cardiac vessels is likely to vary in intensity, depending on which of the above factors is predominant. Thus, if the cardiac vessels are constricted at the same time that arterial pressure is elevated, one of three reactions of the coronary flow is possible: decrease, absence, or increase. This may happen, for example, after reflex influences when the cardiac vessels become constricted as a result of afferent impulses reaching the vasomotor center. If meanwhile arterial pressure remains unchanged or rises only slightly, the reaction of the coronary flow will to some extent reflect the condition of the vessels themselves. However, if constriction of the cardiac vessels is accompanied by elevation of blood pressure, the situation changes. The higher the arterial pressure rises, the more it compensates the decrease in blood flow caused by constriction of the coronary vessels. The result may be a situation in which, despite constriction of the cardiac vessels, the volume of blood flowing through them in a unit of time increases. It is also possible to have a condition when, despite dilation of the coronary vessels by some pharmacological agent, the volume of blood flowing through them in a unit of time, not only does not increase as a result of the simultaneous lowering of blood pressure, but even decreases.

Thus, in all cases in which vasoconstriction or vasodilation is associated with elevation or lowering of arterial pressure, measurement of the volume rate of the coronary flow does not ensure the obtaining of quantitative data on the magnitude of the vascular response to a nerve impulse or action of a humoral agent or drug.

To evaluate the mechanism of action of a pharmacological agent, it is necessary to know whether it is due to the reaction of the coronary vessels themselves or whether it is the result of changes that are meanwhile taking place in the hemodynamics of the organism or in cardiac activity.

In studying the effect of pharmacological agents on cardiovascular reflexes, it is particularly important to distinguish between changes in coronary vascular tone and hemodynamic and extravascular influences. Since changes in the coronary flow in response to stimulation may vary with the predominance of those factors whose interaction determines the level of the myocardial blood supply, the intensity of the effect of the drugs can be evaluated only on the basis of exact information concerning the tone of the coronary vessels. It is necessary, therefore to create the experimental conditions that make it possible to judge changes in resistance of the cardiac vessels regardless of any changes in systemic arterial pressure. This can be done by using special methods of differentiating the various factors that change the coronary blood flow. These methods are based on the principle of perfusing the cardiac vessels while the amount of blood entering the coronary vessels or the pressure is artificially stabilized.

The method we used involves artificially stabilizing the blood flow in the vessels by perfusing them with the animal's own blood, using a special pump to ensure a constant volume of perfusion. The design and operating principle of this apparatus has been described by V. M. Khayutin, V. M. Danchakov and V. L. Tsaturov (1958) (fig. 3).

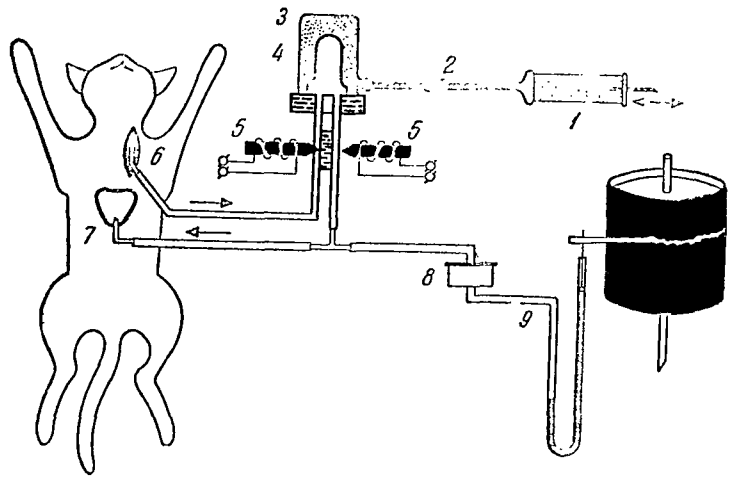


Figure 3. Diagram illustrating the operating principle of a perfusion pump with a constant flow rate for recording vascular resistance.
1--piston pump, drive unit; 2--hydroconductor; 3--working head; 4--rubber cap; 5--electromagnetic valves; 6--tube collecting blood from a carotid artery (pump inlet); 7--tube supplying blood to a coronary artery (pump outlet); 8--quenching device; 9--mercury manometer.

It is evident from figure 3 that the apparatus consists of three main parts--pump drive unit (1), working head (3), and recording manometer (9). These units are interconnected hydraulically and electrically. When the coronary vessels are perfused, blood from the central segment of a carotid artery passes through a cannula (6) into a thin rubber cap (4) within the working head. The hollow part of the working head is filled with water and connected by a hydroconductor (2) to the piston pump of the drive unit (1). The valves (5) are an electromagnetic relay triggered by impulses from the drive unit (1). Due to the movement of the pump piston, which is coordinated with the working of the valves to ensure one-way flow of the blood, the latter proceeds from the carotid artery through the rubber cap into the cannula (7) inserted into the coronary artery. The perfusion pressure is recorded at the pump outlet by the mercury manometer (9). Thus, the perfusion pump, after collecting blood from the animal's artery, forces it into the coronary vessels in a constant volume per unit of time. Under these conditions the pressure recorded at the pump outlet reflects changes in the resistance of the coronary vessels, rising when they constrict and falling when they dilate.

The design of experiments to measure the resistance of coronary vessels is as follows. In acute experiments on cats, the thorax is opened up under the conditions of artificial respiration and 1-1/2 to 5 cm long portions of the 3rd, 4th and 5th ribs are removed from the left side of the thorax. To prevent hemorrhages, ligatures must first be applied to the internal mammary and intercostal arteries. The resistance of the coronary vessels is measured by inserting a specially shaped vinyl chloride cannula into the orifice of the left coronary

artery through the aortic arch. Figure 4 shows autoperfusion of the left coronary artery. The advantages of the method are that the region to be perfused includes the entire system of the left coronary artery through which, according to the literature, the heart receives 85 percent of the inflowing blood. However, the method is not without shortcomings. Insertion of a cannula into the common left coronary artery at the place where it divides into the descending and reflex branches may result in arrhythmia, thereby interfering with the performance of the experiments, or in ventricular fibrillation. These complications almost never arise if the coronary vessels are perfused by introducing a thin polyethylene catheter (0.5-0.6 mm in diameter) into the reflex branch of the left coronary artery (fig. 5). This naturally reduces the area to be perfused. The various problems can be correctly solved by using either method, depending on the particular purpose of the investigation.

For example, in studying the action of pharmacological agents on coronary vascular reflexes, it is more convenient to use the second method because it has less effect on cardiac activity and on the innervation of the coronary vessels. On the other hand, a clearer idea of the effect of the agents on resistance of the coronary vessels may be obtained by perfusing a large portion of the myocardium, i.e., the entire region supplied with blood through the left coronary artery.

Before starting the experiment, the perfusion pump system and the polyethylene cannula are filled with Ringer's solution and heparin solution, respectively. Just before perfusion begins, heparin is injected into the animal intravenously (1000-1500 U/kg). The experiment begins with determination of the blood flow

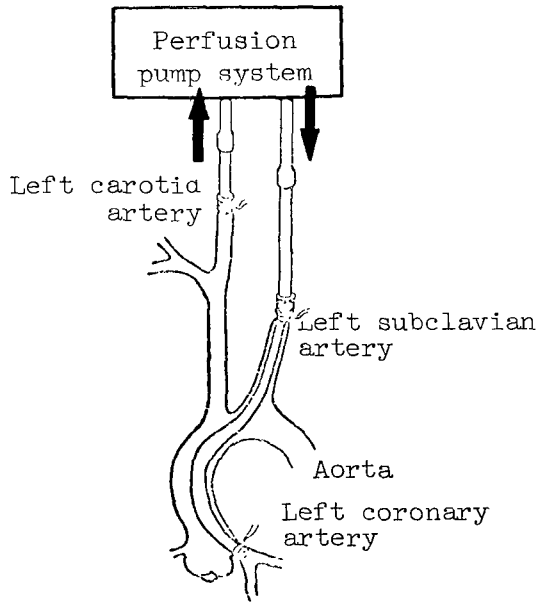


Figure 4. Insertion of a cannula through the aortic arch into the orifice of the left coronary artery.

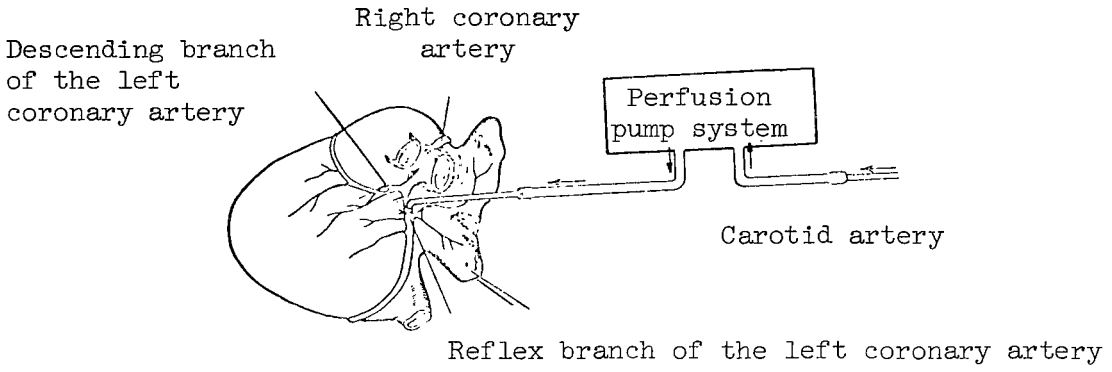


Figure 5. Autoperfusion of the reflex branch of the left coronary artery. The diagram shows the region in which ligatures are applied and a cannula inserted into the reflex branch of the left coronary artery.

rate (i.e., volume of perfusion) needed for the normal myocardial blood supply of the particular animal. This requires selecting that volume of blood to be directed to the coronary vessels whereby the level of perfusion pressure is equal to or a little above the blood pressure level of the animal.

In our experiments perfusion pressure (resistance of the coronary vessels was measured with a mercury manometer simultaneously with arterial pressure (in a carotid or femoral artery). The pharmacological agents under study were injected intravenouslv or directly into the coronary vessels.

Since it was important to determine the degree of involvement of extravascular factors in the mechanism of action of the drugs on the coronary circulation, intraventricular pressure was recorded in several series of experiments. An electrical manometer was used to record pressure in the left ventricle. The induction pickup of the instrument was introduced into the left ventricle through the left auricle and secured with a purse-string suture. Pressure in the ventricle was recorded with an ink-writing recorder. Details on the design of these experiments are given in the appropriate sections. We have already mentioned that a special section discusses the effect of pharmacological agents on coronary vascular reflexes. The experiments aimed at studying such reflexes were performed by the method of resistography. Account was taken of changes in resistance of the coronary vessels and blood pressure after stimulation of the carotid sinus receptors (by occlusion of the carotid artery) and afferent fibers of the tibial and median nerves. After these nerves were divided, immersible electrodes were placed on their central segments. Stimulation was produced by rectangular impulses from an electron stimulator (frequency 50-60 cps, duration 1-2 m/sec, voltage 2-10 v).

In some cases it was necessary to investigate the effect of pharmacological agents on myocardial oxygen consumption and cardiac activity. Oxygen consumption was determined by the photoelectric method, which is based on measuring the amount of oxyhemoglobin in venous blood draining from the carotid sinus. Ye. M. Kreps' oxygenometer was used for continuous measurement of the amount of oxygen in blood draining from the coronary sinus. The procedure for determining

myocardial oxygen consumption by this method in experiments on cats was developed by I. Ye. Kisin (1959). Additional details on the use of the method in our investigations are given below (pp. 81 and 82).

To determine the work performed by the heart, it is necessary, of course, to have information about its output. We therefore ran a special series of chronic experiments on dogs in which we used Grollman's method (1932) in I. I. Khrenov's modification (1946) to measure the cardiac output. Experiments of this kind were essential in studying the effect of chlorazicin on the cardiac blood supply. Details will be found in the section on chlorazicin.

Conclusions on the mechanisms of action of the various pharmacological agents on the coronary circulation were based on a comparison of their influence on a number of indices of the cardiac blood supply. The results of the experiments were statistically processed. The changes in volume rate of the coronary flow, resistance of the coronary vessels, and blood pressure were calculated in percentages of their original values. The mean values were determined in each series of experiments with the standard error and confidence limits (95 percent of the probability level). In studying the effect of pharmacological agents on the coronary vascular reflexes, the significance of the observed changes was determined from the criterion of significance of the mean difference. The degrees of change in the absolute values of the coronary vascular reflexes and blood pressure were calculated in percentages of their original values. In these experiments the mean data were also determined in each series of experiments with the standard error and confidence limits. The results of statistical processing of the experiments were then tabulated and included in the appropriate sections of the book. The following conventional symbols are used in the tables: p--probability of true mean value; n--number of experiments; $f = n^1 + n^2 - 2$; t--Student-Fisher criterion for small samples.

PART I

EFFECT OF PHARMACOLOGICAL AGENTS ON PERIPHERAL REGULATION OF THE CARDIAC BLOOD SUPPLY

CHAPTER 1. EFFECT OF ADRENOMIMETIC AGENTS ON THE CORONARY CIRCULATION

The effect of epinephrine on the cardiac vessels has been extensively investigated since the beginning of the 20th century. It is now an established fact that epinephrine and other adrenomimetic agents dilate the coronary vessels. It is generally believed that the innervation of the cardiac vessels is such that excitation of adrenergic structures results in dilatation rather than constriction of the coronary vessels. However, this view is not adequately supported by experimental data since it is still unclear whether dilatation of the coronary vessels is due to the direct action of epinephrine on them or to associated changes in the hemodynamics and metabolic processes of the myocardium.

Analysis of the literature shows that the data are highly varied, the main reason being that the authors used different methods. Some studied the effect of epinephrine and norepinephrine on smooth muscle, using for their experiments striae of vascular tissue. The response of striae of coronary arteries to epinephrine varies with the species of animal. In most cases adrenomimetic agents contract the muscles (F. P. Trinus, 1959; Barbour, 1912; others). Only striae of the coronary vessels of swine, oxen, and dogs respond to adrenomimetics by relaxing (Cruickshank and Subba Rau, 1927; Smith and Coxe, 1950). Many experiments involved an isolated heart preparation. For example, N. P. Krapkov (1950), studying the preparation of an isolated heart arrested by strophanthin, showed that under these conditions epinephrine does not constrict the coronary vessels. On the contrary, in most cases it dilates them. This was the conclusion of S. P. Zavodskoy (1921), who found that epinephrine dilates the vessels of the isolated heart of the newborn.

Kountz (1932) and Baker (1953) investigated the effect of epinephrine and norepinephrine on drainage from the coronary vessels, perfusing the vessels of the isolated human heart. They found that during the perfusion of a beating heart, epinephrine reduces the drainage from the coronary vessels, but dilates the vessels of the arrested heart.

On the other hand, some authors who used the preparation of the isolated contracting heart and the heart-lung preparation observed that epinephrine intensifies the drainage from the coronary vessels (Markwalder and Starling, 1913, 1914; Melville, 1932; Bagoury and Saalfield, 1934; Katz, Linder, et al., 1938; Kordik, 1951).

Other investigators found that epinephrine constricts the coronary vessels (S. V. Anichkov, 1923; Wiggers, 1909; Barbour and Prince, 1914; Drury and Sumbal, 1924; Hausler, 1929; Saalfield, 1931; Carvalho, 1943).

There is also the view that during perfusion of the vessels of the isolated heart, the action of epinephrine varies with the concentration. In low doses it constricts the coronary vessels, but in large doses dilates them. It was assumed, therefore, that the dilatation observed after the use of large doses results from the changes in cardiac activity that take place at this time (Brodie and Collis, 1911; Gruber and Roberts, 1926; Smith, Miller and Graber, 1926; Leusen and Essex, 1953; Aukut, 1955).

Most of the investigations dealing with the effect of epinephrine on the coronary circulation of the intact organism involved the use of methods based on recording the volume rate of the coronary flow (Wegria, Essex, Herrick and Mann, 1940; Green, Wegria and Boyer, 1942; Eckenhoff, Hafkenschiel and Landmesser, 1947; Brose, Schaefer, et al., 1953; West, Guzman and Bellet, 1957; Nuki, 1957; Jourdan and Faucon, 1958; others). These investigations demonstrated that epinephrine intensifies the volume rate of the coronary flow. They also were the basis for the contention that epinephrine dilates the cardiac vessels.

However, measurement of the volume rate of blood flow in the cardiac vessels is insufficient for evaluating the tone of these vessels because it results from the interaction of several factors, the most important being changes in the level of systemic arterial pressure, cardiac activity, and intensity of myocardial metabolism. Since epinephrine causes marked changes in these factors, the resultant increase in rate of the coronary flow may be the consequence of these changes rather than of its direct influence on the adrenergic structures of the coronary vessels. The only attempts to solve the problem were made by Binet and Burstein (1953) and Berne (1958), who used methods that enabled them to exclude the hemodynamic influence of blood pressure fluctuations and to record the tone of the cardiac vessels. Binet and Burstein conducted their investigations on the heart preparation in situ, while Berne did most of his work on the fibrillated heart.

It is evident from this review of the literature that there is still no consensus on the nature of the effect of epinephrine on the cardiac vessels or on its mechanism of action. It is obvious that the complex and confused subject of the effect of epinephrine and similar drugs on the coronary circulation can be elucidated only by comparing results of experiments in which several methods are used so that the different factors involved can be analyzed. We studied the effect of epinephrine and norepinephrine on the coronary circulation in intact animals, using the method of resistography and recording the volume rate of blood flow. In addition, in some experiments we recorded pressure in the cavity of the left ventricle to analyze the experimental data. Use was made of crystalline preparations of epinephrine and norepinephrine (l-norepinephrine bitartrate) injected intravenously or into the blood stream moving toward the coronary vessels.

The experiments with the resistographic method showed that epinephrine generally has a two-phase action. As soon as the drug is injected, the cardiac

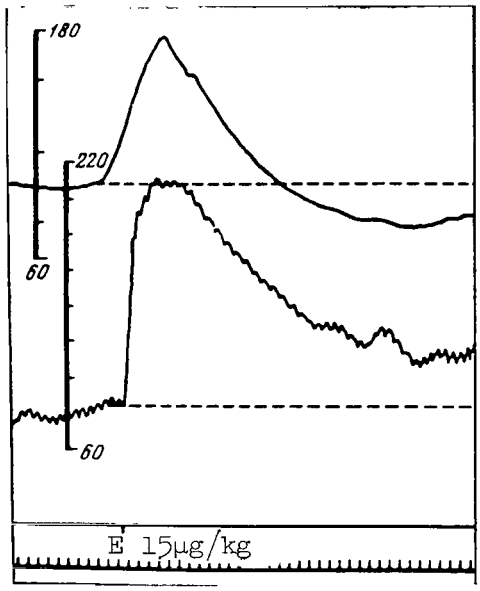


Figure 6. Effect of epinephrine (15 μg/kg) on resistance of the coronary vessels and on blood pressure.
Top to bottom: perfusion pressure--resistance of coronary vessels (resistogram), blood pressure, mark of administration of the agent, time mark--5 sec. Broken lines designate the original level of perfusion and blood pressures.

vessels constrict, after which they dilate. This action is very distinct when the drug is injected into the blood stream moving toward the coronary vessels. The intensity of the phases varies within broad limits.

After intravenous injection of 5 μg/kg of epinephrine, the increase in resistance of the cardiac vessels averaged 10 ± 1.8 percent in 9 experiments. When the dose was increased, its vasoconstrictor effect also increased. After injection of 10 μg/kg of the drug, the increase in resistance of the cardiac vessels averaged 22 ± 3.2 percent in 13 experiments; after injection of 15 μg/kg, the increase averaged 37 ± 4.5 percent in 10 experiments (fig. 6).

The results of this series of experiments are presented in the form of a graph (fig. 7), which shows that increasing the dose of epinephrine intensifies the vasoconstriction phase of its action. The duration of the constriction phase varied from experiment to experiment. For example, after a dose of 5 μg/kg of epinephrine, it lasted about a minute (averaging 57 ± 3.2 sec in 9 experiments). When the dose was increased, this phase lengthened somewhat. For example, after a dose of 15 μg/kg, it increased to 2 min or more in 10 experiments (averaging 160 ± 17 sec). Thus, the intensity and duration of the constriction phase increased with the dose.

The dilatation phase, on the other hand, was highly variable. We were unable to detect any direct connection between its intensity and the dose of

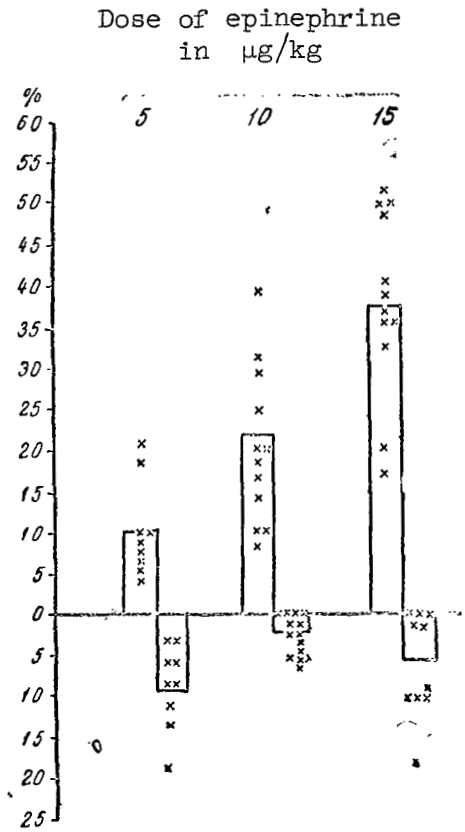


Figure 7. Relationship between intensity of the constriction phase of coronary vessels and dose of epinephrine and variability of their dilatation phase.
Ordinate--changes in resistance of coronary vessels in percentages of the original level. From zero upward--intensity of constriction phase, downward--dilatation phase. Height of columns--mean value of change in resistance in each series of experiments in percentages; x--maximum change in resistance of coronary vessels in percentages in each experiment.

epinephrine used. After injection of 5 μg/kg, the lowering of resistance of the coronary vessels averaged 8.1 ± 1.5 percent in 10 experiments. When the dose was increased, the dilatation phase was even more variable or sometimes was absent altogether. The dilatation phase lasted from 1 to 4-5 min.

Unlike epinephrine, norepinephrine has a rather weak vasoconstrictor effect on coronary resistance. After injection of a dose of 5 μg/kg, the increase in resistance averaged 5 ± 1.3 percent in 7 experiments. A comparison of epinephrine and norepinephrine (in a dose of 5 μg/kg) with respect to vasoconstrictor effect showed that the former increased the resistance of the coronary vessels twice as much as the latter. The difference between the effects was statistically significant ($p < 0.05$).

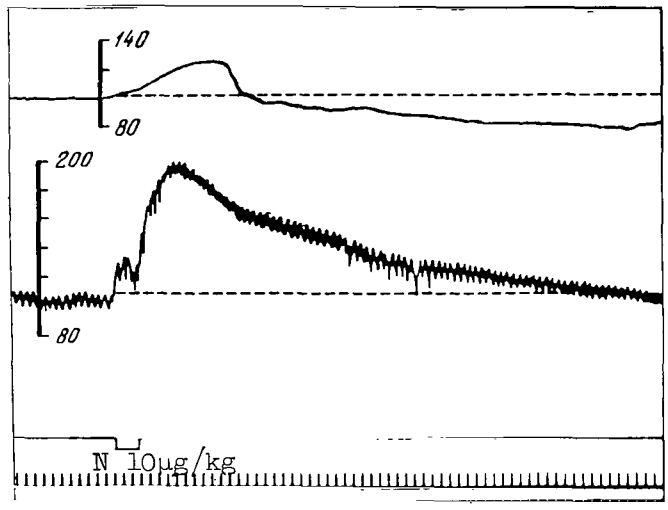


Figure 8. Effect of norepinephrine (10 μg/kg) on resistance of the coronary vessels and on blood pressure.
Top to bottom: perfusion pressure (resistogram), blood pressure, mark of administration of norepinephrine, time mark--5 sec.

The intensity of the dilatation phase was somewhat more pronounced after the action of norepinephrine. This phase occurred in almost every case (unlike that after epinephrine) even though it was sometimes quite brief (no longer than 40-45 sec) (fig. 8).

The results of the experiments summarized in table 1 show that both epinephrine and norepinephrine exert a two-phase effect on the coronary vessels, the latter causing less intense constriction but more regular dilatation. It is interesting to note that constriction of the cardiac vessels under the influence of epinephrine in intact animals was observed only by those authors who used methods that enabled them to exclude the hemodynamic influence of blood pressure fluctuations (Binet and Burstein, 1943; Berne, 1958).

Therefore, it is reasonable to assume that the increase in volume rate of the coronary flow observed immediately after the injection of epinephrine is not evidence of dilatation of the coronary vessels, i.e., lowering of their resistance. It seems clear that pressure increases sharply in the aorta owing to vasoconstriction in other parts of the body so that, despite constriction of the coronary vessels, the rate of blood flow therein may rise.

Since we evaluated the degree of cardiac vascular constriction from the increase in resistance, it was necessary to determine the extent to which the extravascular components of resistance are involved in the vasoconstrictor effect produced by adrenomimetic substances. It is a well known fact that the latter provoke sharp changes in hemodynamics and cardiac action. Hence, it was impossible to exclude the possibility that changes in the extravascular factors play a major role in increasing the resistance of the coronary vessels.

TABLE 1. EFFECT OF EPINEPHRINE AND NOREPINEPHRINE ON RESISTANCE OF THE CORONARY VESSELS AND ON BLOOD PRESSURE. (MEAN DATA IN PERCENTAGES OF THE ORIGINAL LEVEL WITH THE STANDARD ERROR)

Pharmacological agent	Dose in μg/kg	No. of experiments	Constriction phase (increase in resistance) of coronary vessels	Dilatation phase (decrease in resistance) of coronary vessels	Blood pressure
Epinephrine	5	9	10 ± 1.8	8.1 ± 1.5	72 ± 10.7
	10	13	22 ± 3.2	2 ± 0.3	81 ± 13.7
	15	10	37 ± 4.5	6 ± 1.9	131 ± 14.8
Norepinephrine	5	7	5 ± 1.3	11 ± 2.5	28 ± 8
	10	5	16 ± 3.7	7 ± 2.8	54 ± 12.1

To clarify the matter, we performed a series of experiments in which changes in resistance caused by epinephrine and partial aortic occlusion were compared. The method employed increased pressure in the cavities of the heart and, as a result, intensified extravascular resistance. Pressure was recorded in the left ventricle by means of an electric manometer, the induction pickup of which was introduced into the ventricular cavity through the left auricle. A screw-type vascular clamp was used to occlude the aorta. We raised aortic pressure and at the same time raised intraventricular pressure to the same value as that achieved by injecting a given amount of epinephrine. We then compared the amount of increase in coronary vascular resistance (table 2). The table shows that with equal elevation of pressure in the left ventricle, resistance of the coronary vessels under the influence of epinephrine was three times stronger than after occlusion of the aorta. The difference in these effects was statistically significant ($p < 0.05$). One of the experiments is shown in figure 9a, b.

We found, therefore, that the increase in resistance of the coronary vessels under the influence of epinephrine is due mainly to its direct action on the vessels themselves and partly to increase in the extravascular components of resistance. We previously mentioned that epinephrine is more potent than norepinephrine in increasing resistance. The reason may be that norepinephrine injected intravenously causes bradycardia, resulting in a decrease in the stroke volume of the heart. Therefore, despite the increase in perfusion resistance of the vessels, which elevates systemic arterial pressure, cardiac activity changes less under the influence of this drug than it does after the administration of epinephrine (McMichael and Scharpey-Scharfer, 1944; Barcroft and Swan, 1953).

It is reasonable to assume, therefore, that the extravascular components of resistance play a smaller part in manifestation of the effect of norepinephrine on the cardiac vessels than they do after the action of epinephrine, which causes tachycardia and a marked increase in cardiac output and activity. Thus, the difference in rate of change in resistance of the coronary vessels under the influence of epinephrine and norepinephrine is clearly due not to their direct vasoconstrictor effect but to the extent to which the extravascular components of resistance are involved in manifestation of the action of each of the drugs.

TABLE 2. CHANGE IN INTRAVENTRICULAR AND ARTERIAL PRESSURES (IN mm Hg) AND IN PERFUSION PRESSURE (AS A PERCENTAGE OF THE ORIGINAL LEVEL) AFTER ADMINISTRATION OF EPINEPHRINE AND OCCLUSION OF THE AORTA.

No. of experiment	Epinephrine				Norepinephrine			
	Intraventricular pressure	Arterial pressure	Perfusion pressure	Mean change in perfusion pressure with the standard error	Intraventricular pressure	Arterial pressure	Perfusion pressure	Mean change in perfusion pressure with the standard error
1	100	60	17		100	54	7	
2	100	118	50		100	92	15	
3	80	50	43	37 ± 5.5%	80	50	11	12 ± 2.8%
4	60	44	40		60	40	18	
5	120	62	33		120	44	11	

$t = 2.93$; $n = 8$; $p < 0.05$

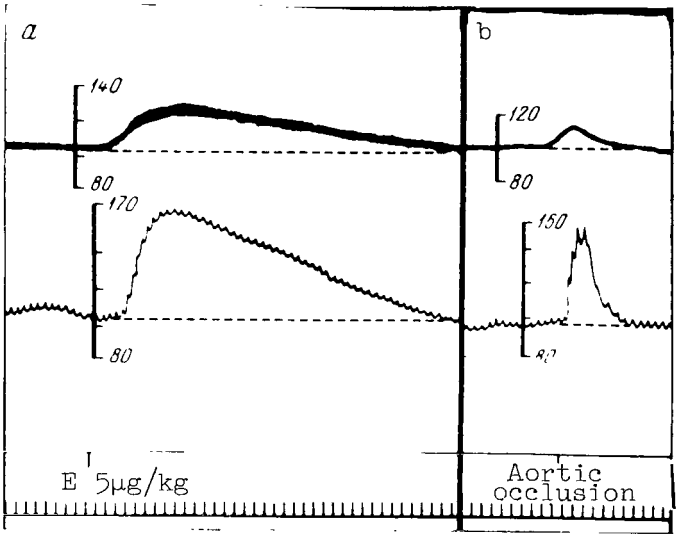


Figure 9a. Changes in resistance of the coronary vessels and blood pressure after the action of epinephrine (a) and occlusion of the aorta (b).
Top to bottom: perfusion pressure (resistogram), blood pressure, mark of administration of epinephrine and occlusion of aorta, time mark--5 sec.

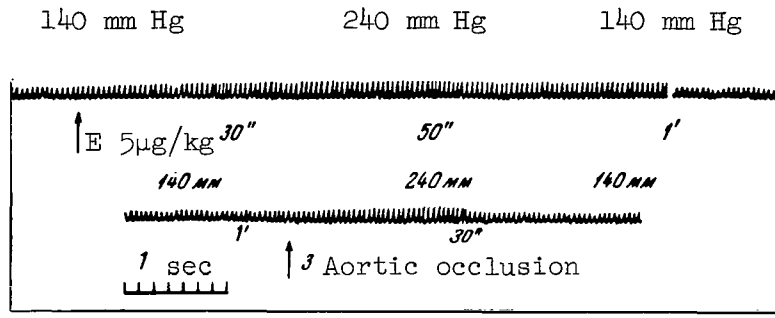


Figure 9b. Recording of pressure in the left ventricle by means of an electric manometer (the same experiment). Top curve--increase in pressure in the left ventricle after administration of epinephrine; bottom curve--the same after occlusion of the aorta. In both cases the increase in pressure amounted to 100 mm Hg. Time mark under curves--length of time the recording instrument stopped (time mark--1 sec).

Our observations provide grounds for believing that the cardiac vessels become constricted as a result of excitation of the adrenergic structures of the coronary vessels by adrenomimetic substances. To verify the assumption, we performed experiments which showed that the vasoconstrictor effect of epinephrine and norepinephrine on the coronary vessels is blocked by adrenolytic substances (dihydroergotamine was used as the adrenolytic--1 mg/kg injected intravenously) (fig. 10). We concluded that the coronary vessels constrict in response to the administration of adrenomimetic substances due to excitation of their adrenergic structures.

Of considerable interest is the origin of the dilatation phase of the cardiac vessels under the influence of epinephrine. The adrenomimetics are known to increase markedly the intensity of myocardial metabolism. Changes in myocardial metabolism under the influence of epinephrine depend largely on the changes that may take place in myocardial oxygen consumption.

A number of investigators found that epinephrine and norepinephrine increase myocardial oxygen consumption (Evans and Ogava, 1914; Evans, 1917; Gollwitzer-Meier, Kramer and Krüger, 1936; Garcia-Ramos and De Arellano, 1951). As myocardial oxygen consumption grows, the volume rate of the coronary blood flow increases (Katz, Williams, Laurent, Bolene-Williams and Feinberg, 1956; Raab, 1956; Feinberg and Katz, 1958; Koroku, Shigei, et al., 1960).

Increase in rate of myocardial metabolism and, above all, in oxygen consumption results from an increase in blood pressure and cardiac activity caused by epinephrine. Changes in hemodynamic conditions seem to be the main, but not the only factor that increases the rate of myocardial metabolism under the influence of adrenomimetic agents. The increase in myocardial oxygen consumption caused by these substances is not proportional to the increase in cardiac activity (Gollwitzer-Meier, Kramer and Krüger, 1936; Gremels, 1936). According to I. Ye. Kisin (1960), who studied the correlation between changes in volume rate

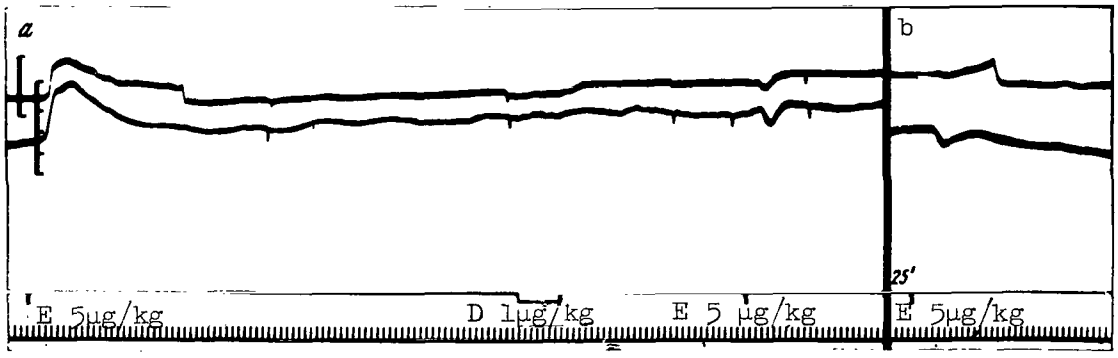


Figure 10. Dihydroergotamine blockade (1 mg/kg) of the vasoconstrictor action of epinephrine (5 µg/kg) on the coronary vessels.
Top to bottom: resistogram, blood pressure, mark of administration of epinephrine, time mark--5 sec. a--effect of epinephrine before and after injection of dihydroergotamine; b--25 min later, start of renewal of the vasoconstrictor action of epinephrine on the coronary vessels.

of the coronary flow and myocardial oxygen consumption under the influence of adrenomimetics, these drugs are capable of increasing to some extent the intensity of the above-mentioned processes, even if systemic arterial pressure is stable. These investigations indicate that the rate of myocardial metabolism under the influence of adrenomimetic agents may be independent of any changes in hemodynamics and cardiac activity that may take place at this time.

Gollwitzer-Meier and Kroetz (1940) found that the rate of blood flow under the influence of epinephrine is 4 times higher in experiments on intact animals and in isolated heart preparations. These investigators believed that in intact animals the increase in volume rate of blood flow after the administration of epinephrine is caused one-third by active dilatation of the coronary vessels, two-thirds by the hemodynamic factor, which intensifies pressure in the coronary arteries and increases the coronary flow.

In summary, the increase in volume rate of the coronary flow under the influence of adrenomimetic agents varies with the increase in myocardial oxygen consumption. The latter, in turn, results from the direct influence of these substances on the energy processes in the myocardium and from the ensuing changes in the hemodynamics of the organism. The increase in coronary flow is insufficient, however, to compensate the myocardial oxygen requirement that grows under the influence of adrenomimetic agents (Gollwitzer-Meier and Kroetz, 1940; Gremels, 1933). Berne (1958) found that epinephrine and norepinephrine in experiments on the fibrillated heart increased myocardial oxygen consumption much more rapidly than they did the rate of coronary flow. The mean increase in blood flow in his experiments was 38 percent, whereas myocardium oxygen consumption was 126 percent above the original level. Under these conditions the heart naturally developed hypoxia. In intact animals, the increasing myocardial oxygen consumption under the influence of epinephrine is presumably ensured to some extent by compensatory hemodynamic mechanisms.

The state of the cardiac blood supply undoubtedly varies from case to case with the effectiveness of these regulatory hemodynamic influences. These considerations led us to conjecture that development of the vasodilatation phase of epinephrine action might be prevented by artificially increasing the myocardial blood supply, i.e., by providing the heart with sufficient oxygen. To check this assumption, we performed experiments in which epinephrine was administered under the conditions of artificially created differences in the rate of the myocardial blood supply. The experiments showed that the dilatation phase of epinephrine action can be completely prevented by using a perfusion pump to increase the volume of blood entering the coronary vessels. However, if small volumes of blood enter the vessels, the magnitude of dilatation increases (fig. 11). It is clear from the figure that with a blood flow rate of 5-8 ml/min, there was a pronounced dilatation phase. When the flow rate was increased to 22.2 ml/min, injection of the same dose of epinephrine into the coronary vessels merely caused them to contract (fig. 11c). The dilatation phase did not occur. The state of the myocardial blood supply obviously plays a decisive role in manifestation of the dilatation phase of the coronary vessels.

If conditions are created to satisfy the myocardial requirements for oxygen, the coronary vessels do not become dilated.

Thus, there is no doubt that development of the vasoconstrictor effect under the influence of epinephrine depends on the intensity of the cardiac blood supply, i.e., on the extent to which the myocardial oxygen requirements are satisfied.

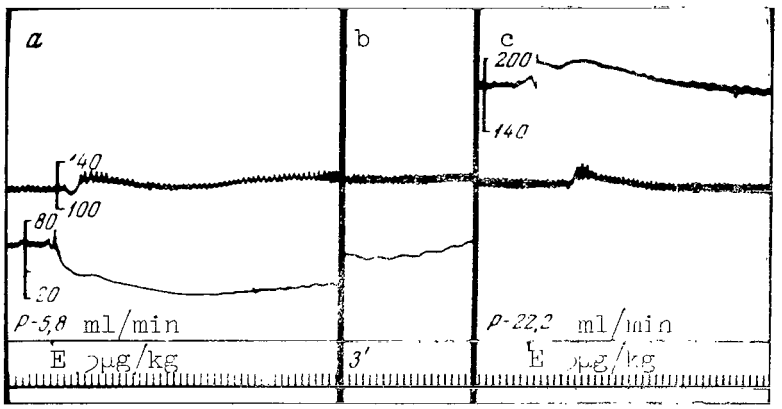


Figure 11. Effect of epinephrine on resistance of the coronary vessels with different rate of cardiac blood supply. a, b--epinephrine (5 μg) injected into the coronary vessels with blood flowing into them at a low rate (5.8 ml/min). Top to bottom: blood pressure, perfusion pressure (resistogram), mark of administration of the agent, time mark--5 sec; c--epinephrine injected into the coronary vessels with blood flowing into them at a high rate (22.2 ml/min). Top to bottom: perfusion pressure, blood pressure, mark of administration of the agent, time mark--5 sec.

This raises the question of whether the level of myocardial metabolism is the only factor in dilatation of the coronary vessels under the influence of adrenomimetic agents or the dilatation phase is due in part to the specific effect of these agents on the adrenergic structures. To resolve the matter, we decided to perform experiments in which epinephrine would be administered following a blockade of the adrenergic structures by dihydroergotamine (1 mg/kg). The conditions of myocardial blood supply were selected in such a manner that dilatation of the cardiac vessels caused by epinephrine would be fairly pronounced. The results showed that dihydroergotamine does not prevent the vessels from dilating (through a lowering of their resistance). However, the intensity of the vasodilator effect of epinephrine after a blockade of the adrenergic structures is considerably reduced. This effect may also be due to decreased participation of extravascular factors in manifestation of the epinephrine action. There is some support for this view from the fact that dihydroergotamine blocks the action of epinephrine on blood pressure as well as on the rhythm and force of cardiac contractions. Under these conditions cardiac work does not increase and the change in rate of myocardial metabolism obviously is insignificant. Thus, the increase in myocardial oxygen consumption and resultant acceleration of the volume rate of the coronary blood flow seem to be caused mainly by the heavier load placed on the heart by epinephrine due to elevated systemic arterial pressure.

The above-described observations do not, of course, exclude the possibility that the influence of epinephrine on the adrenergic structures is a factor in the development of the vasodilatation phase of its action. Moreover, adrenolytic agents do not block all the cell receptors capable of reacting with epinephrine and norepinephrine (Ahlquist, 1958). However, the distinct relationship noted in our experiments between the development of the dilatation phase of the coronary vessels and the conditions of the myocardial blood supply supports our view that the main factor responsible for dilatation of the coronary vessels under the influence of epinephrine is the increased rate of myocardial metabolism. Additional confirmation comes from the variability observed in the dilatation phase and from the lack of a direct connection between the intensity of the vasodilator effect and the dose of epinephrine used. Thus, it is fair to say that coronary vasodilatation is due not to the direct action of epinephrine but to changes in myocardial metabolism.

The ways in which changes in myocardial biochemical processes induced by epinephrine result in relaxation of coronary smooth muscles is a fairly complex matter, one requiring special study. The published data do not warrant more than a few conjectures regarding the possible underlying mechanism.

Epinephrine and similar substances are known to induce myocardial hypoxia and cause anaerobic breakdown of carbohydrates. Many investigators have noted that the glycogen reserves decrease while the lactic acid concentration of the myocardium rises following the administration of epinephrine (Ye. S. Rozovskaya, 1941; M. Ye. Rayskina, 1951; Fieschi, 1933; Wiecker, 1936; Boque, Evans and Gregory, 1937). Mohme-Lundholm (1953) and Lundholm (1956) found that epinephrine relaxes coronary smooth muscles while increasing the lactic acid content. Substances that block the release of lactic acid completely prevent the vasodilator effect. The authors concluded that the vasodilator effect of epinephrine is due to the accumulation of lactic acids in the cells.

Of interest in this connection are the observations of Ellis (1956) who noted intensified glycogenolysis in all the organs in which epinephrine causes smooth muscle to relax (skeletal muscles, heart, spleen, etc.). Mohme-Lundholm's hypothesis was criticized later because, according to some investigators, epinephrine-induced smooth muscle relaxation is accompanied by a distinct increase in the lactic acid content (Furchgott, 1955; Bentley, 1956).

Burn and Bulbring (1956) and Shanes (1958) found that epinephrine increases the quantity of potassium ions in the cells. Shanes assumes that the products of glycogenolysis which accumulate in the tissues under the influence of epinephrine are acid and therefore help to increase the concentration of cations in the cells, mainly of potassium, resulting in a growth of membrane potential. It is evident from the data cited that the mechanism of relaxing action of epinephrine on smooth muscle is still obscure. It should be noted, however, that the various hypotheses advanced are generally based on the view that glycogenolysis is the main link in the complex chain of reactions that lead to this effect. Our observations on the relationship between the vasodilator phase of epinephrine action on the cardiac vessels and the conditions of the myocardial blood supply are in agreement with these ideas.

In summary, it seems to be an established fact that epinephrine and norepinephrine have a two-phase effect on the cardiac vessels: coronary vasoconstriction immediately after administration followed by dilatation. Our observations and some published data suggest that the constriction phase is due mainly to the direct influence of epinephrine on the adrenergic structures of the coronary vessels, whereas the dilatation phase is caused by epinephrine-induced changes in myocardial metabolism.

Analysis of our own observations and of the literature reveals that the effect of adrenomimetic agents on the coronary circulation as a whole is about as follows. Immediately after epinephrine is injected intravenously, blood pressure rises sharply and cardiac activity changes. The blood vessels of the heart and of most of the other organs respond to the drug by exciting the adrenergic structures, which results in vasoconstriction. However, the heart is placed in a special situation. Despite coronary vasoconstriction, elevated aortic pressure may help to increase the volume of blood passing through the vessels in a unit of time.

Under the influence of epinephrine the myocardial metabolic rate increases. This effect, reflected mainly in increased myocardial oxygen consumption, is intensified by the growing amount of cardiac activity. The cardiac blood supply becomes insufficient to provide for the myocardial oxygen requiresents. The resultant hypoxia causes an anaerobic breakdown of carbohydrates and an accumulation of glycogenolytic products in tissues. This stage is clearly an important link in the chain of reactions that lead to the second phase of epinephrine action--dilatation of the coronary vessels.

In the healthy organism, constriction of the coronary vessels due to epinephrine has no effect on the cardiac blood supply presumably because it is subjected to varied and delicate regulation. But with a change in elasticity of the vascular wall, when the capacity of the vessels to dilate is reduced

(e.g., in atherosclerosis), the vasoconstrictor component may predominate in the effect of the adrenomimetics. The hypoxia developing in the myocardium then results in marked impairment of its blood supply. This assumption has been confirmed by clinical observations of epinephrine promoting attacks of angina pectoris.

CHAPTER 2. EFFECT OF CHOLINERGIC AGENTS ON THE CORONARY CIRCULATION

1. Acetylcholine and Carbachol

The effect of acetylcholine and other cholinomimetic agents on the cardiac vessels has been extensively investigated. However, neither the nature of the changes produced in the coronary circulation by these substances nor the part played by their direct influence on the coronary vessels has as yet been precisely determined. The main reason for this is that they cause drastic changes in hemodynamics and cardiac activity which create technical difficulties in investigating the subject.

The literature is contradictory. In experiments on isolated heart preparations, several investigators noted that acetylcholine dilated the coronary vessels (Wiggers, 1908; Sumbal, 1924; Smith, Miller and Graber, 1926). Other investigators, however, found that it reduced the outflow from the coronary vessels (Epinger and Hess, 1909; Hochrein and Keller, 1931; Katz, Linder, Weinstein, Abramson and Jochim, 1938; A. N. Poskalenko, 1948). Some believe that the difference in acetylcholine effect is due to the concentration of the substance and to the species of experimental animals used.

In experiments on intact animals, most investigators noted that the volume rate of the coronary flow increased after administration of acetylcholine, carbachol, and other cholinomimetic agents (Anrep and Segall, 1926; Wedd, 1936; Wegria, 1937; Essex, Wegria, Herrick and Mann, 1940; Winbury and Green, 1952; Schofield and Walker, 1953; Schreiner, Berglund, Borst and Monroe, 1957; Denison and Green, 1958). Judging by the results of these investigations, the effect regularly occurred when small amounts of acetylcholine were injected directly into the coronary vessels. But in some instances acetylcholine decreased the coronary flow (Rein, 1931; Wegria, Essex, Herrick and Mann, 1940; Eckenhoff, Hafkenschiel and Landmesser, 1947).

These apparently contradictory data were apparently due to the difference in methods used by the various authors. It is a well known fact that the rate of coronary flow is a function of the interaction of several factors, the most important being cardiac activity and blood pressure level. Changes in these factors were the reason for the inconsistency of the results obtained. For example, Arnulf and Buffard (1960) used the method of arteriography. They found that acetylcholine dilated the coronary vessels. It is clear from the literature that at each stage in the development of methods, investigators were confronted with the old and still insufficiently studied matter of the effect of acetylcholine and other cholinomimetic agents on the coronary circulation. It occurred to us that a comparison of the changes in resistance of the coronary vessels and volume rate of the coronary flow following the administration of

acetylcholine and carbachol might provide fairly accurate information about the effects of these drugs on the dynamics of the coronary circulation.

We performed two series of experiments. In the first series we recorded changes in the volume rate of blood flowing from the coronary sinus after intravenous injection of acetylcholine and carbachol. The results showed that acetylcholine in a dose of 1 μg/kg generally reduced the flow within 1-2 min. Moreover, this decrease coincided with the maximum lowering of blood pressure caused by acetylcholine. The extent of the decrease in rate of coronary flow was highly variable (fig. 12). Statistical processing of the data of 7 experiments revealed that the decrease in outflow averaged 21 ± 9.2 percent. In some cases acetylcholine did not reduce the blood flow. It did, however, increase the coronary flow.

However, as mentioned above, in most of the experiments, the injection of acetylcholine was followed by a decrease in the rate of coronary flow, followed 3-5 min later by an increase amounting to 26 ± 1.6 percent (when administered in in a dose of 1 μg/kg). The effect did not last more than 4-5 min. When acetylcholine was administered in large doses, the decrease in rate of blood flow was more pronounced. For example, in a 2 μg/kg dose it reduced the outflow of blood from the coronary sinus 33 ± 2.8 percent (mean of 5 experiments). It will be noted that this dose caused sharp hypotension. The phase of increased flow under these conditions, however, was less pronounced or absent altogether. In the same experiments it averaged 19 ± 1.3 percent.

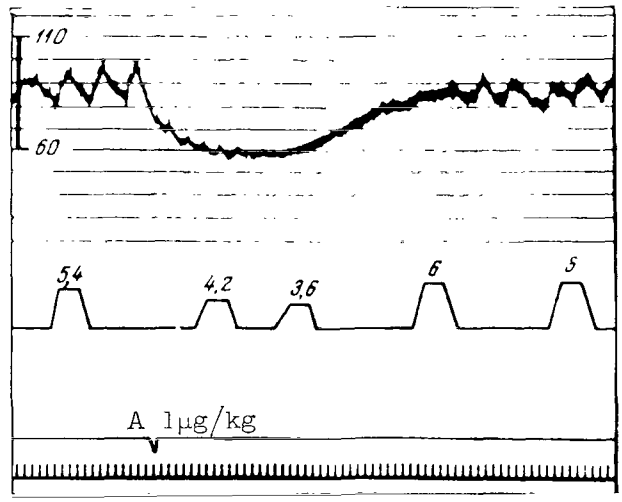


Figure 12. Decrease in volume rate of the coronary flow after injection of acetylcholine (1 μg/kg) and then increase in the rate.
Top to bottom: blood pressure, volume rate of coronary flow (height of columns--extent of coronary flow in 15 sec; figures above the columns--minute volume of blood flow), mark of administration of the agent, time mark--5 sec.

TABLE 3. EFFECT OF ACETYLCHOLINE AND CARBACHOL ON THE VOLUME RATE OF THE CORONARY FLOW AND ON BLOOD PRESSURE. (MEAN DATA IN PERCENTAGES OF THE ORIGINAL VALUES WITH THE STANDARD ERROR)

Agent	Dose in μg/kg	Decrease in volume rate of coronary flow	Change in blood pressure during phase of decreased coronary flow	Increase in volume rate of coronary flow	Blood pressure during phase of increased coronary flow
Acetylcholine	1	-21 ± 9.2	-32 ± 3.8	+26 ± 1.6	- 6 ± 2.6
	2	-33 ± 2.8	-38 ± 2.9	+19 ± 1.3	- 7 ± 1.8
Carbachol	1	-28 ± 4.1	-31 ± 6.2	+28 ± 6.6	- 5 ± 2.5
	2	-29 ± 4.6	-33 ± 3.9	-	-14 ± 1.7

The results of the experiments with carbachol did not differ in principle from those with acetylcholine. In a 1 μg/kg dose it elicited a two-phase reaction. A decrease in blood flow, averaging 28 ± 4.1 percent of the original level in 6 experiments, gave way to an increase averaging 28 ± 6.6 percent. A 2 μg/kg dose caused a decrease of 29 ± 4.6 percent (mean of 6 experiments). There was either no increase in the rate of blood flow in these experiments or it was insignificant. The results of the experiments are summarized in table 3.

It is evident from the table that the phase of decreased volume rate of the coronary flow under the influence of acetylcholine and carbachol coincided with the maximum lowering of blood pressure. The phase of increased coronary flow, on the other hand, coincided with the period when the hypotension induced by the cholinomimetics had almost completely disappeared. Only after administration of a 2 μg/kg dose of carbachol, when hypotension was more pronounced and persistent, was there no phase of increased volume rate of the coronary flow.

In the second series of experiments we recorded changes in resistance of the coronary vessels after administering acetylcholine and carbachol. The results showed that these substances are capable of decreasing the resistance of the cardiac vessels. For example, acetylcholine in as low a dose as 0.5 μg/kg decreased it by 10 ± 1.4 percent of the original level (mean data of 10 experiments). When the dose was increased to 1 μg/kg, the decrease was 15 ± 1.7 percent (mean data of 10 experiments). The effect did not persist more than 2 or 3 min. The results of one of these experiments are presented in figure 13.

The results were about the same after the administration of carbachol, which in a dose of 0.5 μg/kg decreased resistance by 13 ± 1.9 percent of the original level (mean of 5 experiments); in a dose of 1 μg/kg, by 18 ± 1.7 percent. Its effect was longer lasting (5-6 min). The results are presented in table 4.

Thus, the results of the experiments using the method of resistography showed that resistance of the cardiac vessels decreases following the injection of cholinomimetic substances.

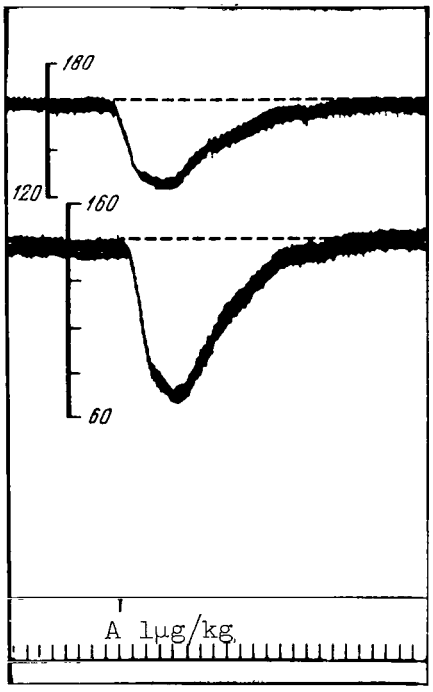


Figure 13. Effect of acetylcholine (1 μg/kg) on resistance of the coronary vessels and on blood pressure.
Top to bottom: perfusion pressure, blood pressure, mark of administration of the agent, time mark--5 sec.

TABLE 4. EFFECT OF ACETYLCHOLINE AND CARBACHOL ON RESISTANCE OF THE CORONARY VESSELS AND ON BLOOD PRESSURE. (MEAN DATA IN PERCENTAGES OF THE ORIGINAL LEVEL WITH THE STANDARD ERROR)

Agent	Dose in μg/kg	No. of experiments	Change in resistance of coronary vessels	Change in blood pressure
Acetylcholine	0.5	10	-10 ± 1.4	-30 ± 1.8
	1	10	-15 ± 1.7	-38 ± 1.0
Carbachol	0.5	5	-13 ± 1.9	-34 ± 4.8
	1	6	-18 ± 1.7	-43 ± 5.7

Since the injection of cholinomimetic substances sharply lowers blood pressure and alters cardiac activity, a decrease in the extravascular components of resistance may play a part in the reduced resistance. A third series of experiments was performed to study this possibility. In these experiments we compared the lowering of resistance of the coronary vessels induced by acetylcholine with changes in their resistance following partial compression of the inferior vena cava. This method limits the flow of blood to the heart,

TABLE 5. CHANGE IN INTRAVENTRICULAR AND ARTERIAL PRESSURES (IN mm Hg) AND IN PERFUSION PRESSURE (IN PERCENTAGES OF THE ORIGINAL LEVEL) FOLLOWING THE ADMINISTRATION OF ACETYLCHOLINE AND RESTRICTION OF THE FLOW OF BLOOD TO THE HEART.

No. of experiment	Acetylcholine				Restriction of blood flow to the heart				
	Intraventricular pressure	Arterial pressure	Perfusior pressure	Mean, percentage of changes in perfusion pressure	Intraventricular pressure	Arterial pressure	Perfusion pressure	Mean, percentage of changes in perfusion pressure	Significance level
1	40	44	29		40	40	12		$p < 0.05$
2	60	26	12		60	30	4		$t = 2.65$
3	100	38	16	19 ± 3.6	100	28	6	8 ± 1.9	$n = 6$
4	120	40	19		120	50	11		

lowers pressure in its cavities, and, as a result, decreases the extravascular component of resistance. We restricted the flow of blood to the heart by lowering intraventricular pressure to the same extent as after the administration of acetylcholine, thus enabling us to compare the degree of reduction in perfusion pressure, i.e., resistance of the coronary vessels. Pressure in the left ventricle was recorded with an electric manometer. A screw coronary clamp was used to compress the vein. The results of this series of experiments are shown in table 5.

The investigations showed that with equal lowering of pressure in the left ventricle, resistance in the coronary arteries decreased much more sharply after the administration of acetylcholine than after compression of the inferior vena cava. Processing of the data revealed that the average decrease in coronary resistance (4 experiments) after the administration of acetylcholine was more than double that caused by restricting the flow of blood into the heart. The difference in these effects was statistically significant with a significance level of $p < 0.05$.

It is thus fair to say that acetylcholine acts directly on the cardiac vessels, although the decrease in the extravascular components of resistance plays some part in realization of the effect.

Special experiments showed that after the administration of atropine (0.5-1 mg/kg) cholinomimetic agents have no effect on the coronary vessels (fig. 14). Thus, dilatation of the cardiac vessels is due to the specific action of these substances on the m-cholinoreactive structures. These data apparently contradict the idea that the vagus nerves do not take a direct part in nervous regulation of the cardiac vessels. However, according to some investigators, the cardiac vessels may be dilated as a result of impulses reaching them along the

cholinergic fibers that form part of the sympathetic nerves. For example, Folkow, Haeger and Uvnäs (1948) found that stimulation of the stellate ganglia in experiments with perfusion of the cardiac vessels causes a substance with the biological properties of acetylcholine to appear in the perfusate. These observations indicate that the sympathetic cholinergic fibers take part in regulating the blood flow in the cardiac vessels. This was also the conclusion of Kiss and Szentivanyi (1958) who used the technique of selective stimulation of individual fibers of the cardiac sympathetic nerves. According to their observations, these nerves include fibers of cholinergic nature which transmit vasodilator impulses to the coronary vessels.

These data suggest that the decrease in resistance of the coronary vessels caused by acetylcholine is linked to the fact that it acts on the cholinoreactive structures which transmit excitation from the vasodilator sympathetic fibers to the cardiac vessels. There is also another possible explanation. Acetylcholine is known to cause vasodilator effects in those organs whose vessels have been deprived of their cholinergic innervation, e.g., kidneys and small intestine (Hunt, 1918; Bulbring and Burn, 1935). Here, too, the action of acetylcholine is characteristically blocked by atropine and realized, therefore, through the cholinoreactive structures of the smooth muscles in the vessels. Hence, it is reasonable to believe that the vasodilator effects of acetylcholine are not always due to the presence of specific vasomotor fibers.

Investigations showed that acetylcholine and carbachol are capable of dilating the coronary vessels. However, it was found in experiments in which the volume rate of the coronary flow was recorded that the maximum decrease in resistance of the coronary vessels generally coincided with the phase of decreased blood flow caused by acetylcholine. These apparent contradictions can easily be reconciled. Acetylcholine sharply dilates the blood vessels in most vascular regions, causing hypotension. Under these conditions, a marked lowering of aortic pressure may reduce the volume of blood passing through them in a unit of time, despite the dilatation of the coronary vessels. This was confirmed by our observations that acetylcholine and carbachol in relatively low doses (which do not seriously impair hemodynamics and cardiac activity) only increase rather than decrease the coronary blood flow. It is now easy to understand the differences in the effects of acetylcholine when administered in various ways. Most investigators who observed a distinct increase in the rate of coronary flow injected the drugs in low concentrations directly into the coronary vessels (Essex, Wegria, Herrick and Mann, 1940; Winbury and Green, 1952; Schofield and Walker, 1953; others). Under these conditions there were no sharp changes in hemodynamics to modify the effect of acetylcholine.

When the dose of a cholinomimetic agent is increased, the coronary flow clearly decreases, and the phase of increase becomes less pronounced and at times is even absent. The ensuing hypotension and changes in cardiac activity result in less blood than usual passing through the coronary vessels in a unit of time, despite their dilatation.

Thus, according to our observations, cholinomimetic agents affect the coronary circulation as follows. Acetylcholine and carbachol injected intravenously dilate the coronary vessels. This effect is due to their action on the

cholinoreactive structures of the cardiac vessels. However, owing to the marked changes these substances induce in hemodynamics and cardiac activity, the myocardial blood supply conditions may not improve. The cardiac blood supply will obviously increase only if the drugs are administered in low doses that do not significantly change the hemodynamic situation.

2. Atropine

Atropine has long been used for acute coronary insufficiency. The theoretical basis for its clinical use rests on the observations of a number of authors who found that tonic vasoconstrictor impulses are transmitted to the coronary vessels along the vagus nerve (Morawitz and Zann, 1912; Anrep and Segall, 1926; Rein, 1931-1932; Gollwitzer-Meier and Krüger, 1935). It is justified, therefore, to use atropine to block the influence of the vagus nerve on the cardiac vessels. But, as mentioned above, the recent investigations of authors who used new techniques showed that the vagus nerve clearly does not participate directly in nervous regulation of the cardiac vessels (Schreiner, Berglund, Borst and Monroe, 1957; Denison and Green, 1958; Wang, Blumental and Wang, 1960).

These data warrant a reconsideration of the influence exerted by atropine on the coronary circulation. There are few references to the subject in the literature. For example, Wegria et al. (Wegria, Essex, Herrick and Mann, 1940; Essex, Wegria, Herrick and Mann, 1940), who studied the effect of atropine on the volume rate of the coronary flow in experiments on anesthetized and non-anesthetized dogs found that there was a marked increase in the coronary flow without accompanying changes in systemic arterial pressure after intravenous injection of the drug.

Later Essex, Herrick, Mann and Baldes (1943) found that denervation of the heart did not block the action of atropine, whereas bilateral vagotomy did so completely. Scott and Balourdas (1959) came to the same conclusion in experiments on dogs in which they recorded the blood flow in the coronary vessels using the nitrous oxide method. They found that atropine intensified the volume rate of the coronary flow as much as bilateral vagotomy. In addition, tachycardia of the same intensity developed.

Nuki (1957) investigated the effect of several pharmacological agents, including atropine, on the coronary circulation, using various methods: recording of the coronary inflow with a bubble flowmeter and outflow from the cardiac vessels in intact animals, in the heart-lung preparation, and on the isolated heart. According to his data, atropine in doses of 0.12-0.15 mg/kg in experiments on intact cats increased the volume rate of the coronary flow only slightly and in experiments on the isolated heart had virtually no effect on the outflow from the coronary vessels. M. S. Vovsi (1957) presents data obtained in his laboratory by Ye.. B. Novikova, who observed that atropine in experiments on cats provoked no distinct changes in the coronary flow that could be recorded with a bubble flowmeter.

Analysis of the literature reveals that an increase in the volume rate of the coronary flow under the influence of atropine is more pronounced in dogs

than in cats, apparently because the vagus nerves in the former have a higher tone.

It is evident from the data cited that the information in the literature on atropine is not of a systematic character. Yet a study of its effect on the cardiac blood supply is valuable not only in elucidating its mechanism of action but in using it properly in the clinic.

We performed two series of experiments, one to record the volume rate of the coronary flow, the other to determine the resistance of the coronary vessels. We hoped that a comparison of the changes in the various parameters governing the myocardial blood supply would enable us to gain a deeper insight into the effect of atropine on the coronary circulation. The experiments demonstrated that atropine is capable of increasing the volume rate of the coronary flow. When injected in a dose of 0.5 mg/kg, the rate increased slightly (7-10 percent above the original level); when injected in a dose of 1-2 mg/kg, the rate rose to 12-20 percent. Statistical processing of the experiments in which a 1 mg/kg dose was used showed that the increase in volume rate of blood flow in the cardiac vessels averaged 13 ± 3.8 percent in 8 experiments. A further boost in the dose had no effect.

Blood pressure was little affected by atropine. The changes averaged 4 ± 2.7 percent in 8 experiments after a dose of 1 mg/kg.

Study of the effect of atropine on the resistance of the cardiac vessels showed that the drug had little effect. In doses of 0.5-1 mg/kg it decreased resistance only by 5-10 percent of the original level. In a dose of 1 mg/kg the decrease in resistance averaged 7 ± 1 percent in 8 experiments.

Thus, we concluded that atropine has but a slight effect on the cardiac blood supply. It increases the volume rate of the coronary flow and weakens the tone of the coronary vessels, but does not significantly change the level of systemic arterial pressure. Table 6 presents the data of both series of experiments with atropine.

To determine whether the decrease in resistance of the coronary vessels caused by atropine is due to its direct action on the coronary vessels or to elimination of the effects of the vagus nerves, we performed experiments in which atropine was injected (1 mg/kg) after bilateral vagotomy. Under these conditions atropine had no effect on the coronary vessels. We obtained similar results in experiments in which we recorded the volume rate of the coronary flow. In only a few experiments was there a decrease in the flow and it was paralleled by a drop in blood pressure that evidently resulted from it (fig. 15c).

The results of our experiments are consistent with the observations of Essex et al. (1940) and those of Scott and Balourdas (1959). There can be no doubt, therefore, that atropine increases the myocardial blood supply by eliminating the influence of the vagus nerves on the heart. It does not follow, however, that its effect is due to dilatation of the coronary vessels owing to their liberation from the vasoconstrictor impulses of the vagus nerves.

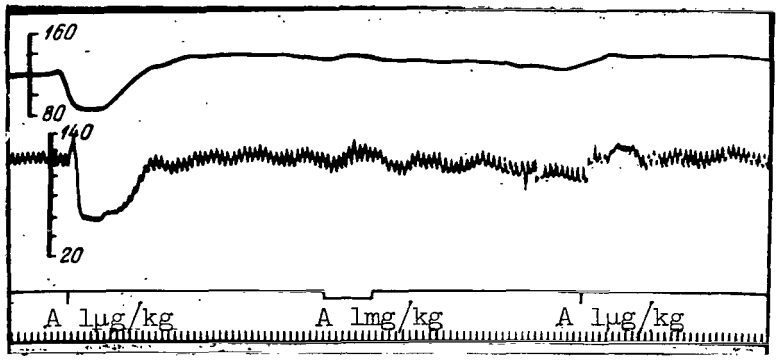


Figure 14. Blocking with atropine (1 mg/kg) of dilating action of acetyline (1 μg/kg) on coronary vessels.
From top to bottom: perfusion pressure (resistogram), blood pressure, introduction of substance, time--5 sec.

TABLE 6. EFFECT OF ATROPINE ON THE VOLUME RATE OF THE CORONARY FLOW, RESISTANCE OF THE CORONARY VESSELS, AND BLOOD PRESSURE. (MEAN DATA IN PERCENTAGES OF THE ORIGINAL VALUES WITH THE STANDARD ERROR)

Agent	Dose in mg/kg	Change in volume rate of coronary flow	Change in resistance of coronary vessels	Change in blood pressure
Atropine	1	+13 ± 3.8 +4.4 - +21.6[1]	-7 ± 1 -10.8 - -3.2[1]	-4 - 2.7 -14.2 - +6.2[1]

[1]Confidence limits.

Scott and Balourdas (1960) convincingly showed that the increase in rate of coronary flow caused by atropine and vagotomy is the result of the accelerated rate of cardiac contractions that develops in both cases. They found that there was no increase in the rate of the coronary flow in dogs with a chronic atrioventricular block of the cardiac conduction system in which atropine did not accelerate the rate of ventricular contractions. They obtained similar data in experiments on vagotomized dogs.

It is a known fact that an increase in the cardiac rate causes an increase in the volume rate of the blood flow in the coronary vessels (Laurent, Bolene-Williams and Katz, 1956; Maxwell, Castillo, White, Crumpton and Rowe, 1958; Gorlin, 1958; Scott and Balourdas, 1959). Laurent et al. showed that the increase in volume rate of the coronary flow during acceleration of cardiac activity is caused by intensified myocardial metabolism, specifically, by increased

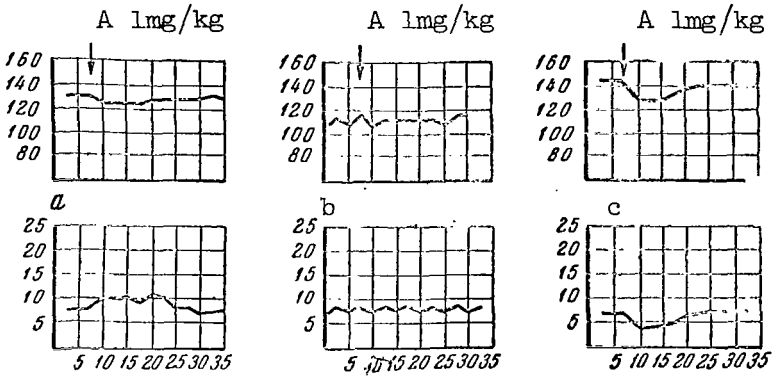


Figure 15. Effect of atropine (1 mg/kg) on the volume rate of the coronary flow under normal conditions (a) and after bilateral vagotomy (b and c).
b--Absence of changes in the coronary flow and in blood pressure after injection of atropine following vagotomy; c--decrease in volume rate of the coronary flow and lowering of blood pressure after injection of atropine following vagotomy. Ordinate: top graphs, blood pressure in mm Hg; bottom graphs, volume rate of the coronary flow in ml/min. Abscissa, time in min.

myocardial oxygen consumption. By blocking the transmission of excitation from the vagus nerves to the heart, atropine accelerates the cardiac rate, which results in an increased volume rate of the blood flow in the cardiac vessels.

In summary, atropine is capable of slightly increasing the cardiac blood supply. In our experiments this effect was not too pronounced. It varies with the tone of the vagus nerves. The effect of atropine, which is dependent on the elimination of vagus influence on cardiac activity, is apparently due to intensification of myocardial metabolism and resultant acceleration of the cardiac rate. Thus, atropine has no direct effect on the heart and the changes that it brings about in the myocardial blood supply are secondary to its acceleration of the cardiac rate.

In using atropine in the clinic, it seems to us that one should take into account the mechanism by which it increases the cardiac blood supply because the intensity of its effect is directly related to increase in the cardiac rate. The clinical effectiveness of atropine in treating coronary disorders may well be due to its capacity to inhibit reflex influences on the heart mediated by the vagus nerves.

CHAPTER 3. EFFECT OF GANGLION-BLOCKING AGENTS ON THE CORONARY CIRCULATION

Agents that block the transmission of excitation in the autonomic ganglia are now widely used in the treatment of hypertension and disorders of the peripheral circulation. An unusually large place is accorded the study of the hypotensive action of these agents in the extensive literature dealing with their pharmacology and clinical aspects. According to the prevalent ideas, the mechanism of action of these drugs is fairly complex, with a number of factors involved. The transmission of excitation to contractile elements of the blood vessels is inhibited by a block of the sympathetic ganglia, resulting in vasodilatation (Paton, 1951, 1952; Gilmore, Kopelman, et al., 1952; Moyer et al., 1952; Moyer, Miller and Ford, 1953; Freis, Rose, et al., 1953; others).

However, this mechanism is not the only one involved in the complex hemodynamic changes that take place in the organism following the administration of ganglion-blocking agents. The latter generally reduce the cardiac output considerably. This was the basis for the view that the hypotensive action of the ganglion-blocking agents is related more to the decrease in cardiac activity than to the lowering of peripheral resistance of the blood vessels (Werko, 1951; Freis et al., 1953). There is also some evidence that the gangliolytics are capable of inhibiting the vasomotor center (P. P. Denisenko, 1953).

Many investigators attach considerable significance in the mechanism of the hypotensive effect of the ganglion-blocking agents to the reduction in venous flow to the heart caused by decreased venous tone (Restall and Smirk, 1952; Jams, Coulter and Saunders, 1953; Smith and Hoobler, 1956). The decrease in venous flow is the reason for the variable intensity of hypotension in relation to bodily position following the action of these drugs. Moreover, the mechanism of hypotensive effect varies from drug to drug. For example, hexamethonium and pentamine (methylaminodiethylene bis ethyldimethyl ammonium bromide) clearly lower blood pressure chiefly by reducing the peripheral resistance of the blood vessels.

The changes that the drugs induce in cardiac activity play a smaller part (Rakita and Sancetta, 1953; Moyer and Handley, 1955). Pentolinium, on the other hand, has no significant effect on the peripheral resistance of the arteries, but it sharply decreases venous tone (Smith and Hoobler, 1956). Marked changes take place in hemodynamics under the influence of ganglion-blocking agents. A new level of blood supply is established in the organs and systems of the body.

We shall not go into detail on the changes in the blood supply of different organs following the administration of ganglion-blocking agents because the

subject is systematically reviewed in Aviado's article (1960). We should like to point out that analysis of the available data on the hemodynamic effects of the gangliolytics reveals that they reduce the volume rate of the blood flow in most vascular regions (kidneys, abdomen, brain) (Ford, Moyer and Spur, 1953; Moyer et al., 1956; Crumpton, Rowe, Capps, Whitmore and Murphy, 1955).

The vessels in the extremities are an exception in that the blood flow there generally accelerates (Hoobler, Neligh, Moe, Malton, Cohen, Ballantine and Lyons, 1945; Slaughter, Brown and Wakim, 1948; Freis, Rose, Partenope, Higgins, Kelly, Schaper and Johnson, 1953; others). For this reason the ganglion-blocking agents are widely used in the treatment of circulatory disorders in the extremities. Calculation of changes in vascular resistance in different organs after administration of these drugs showed that it decreases somewhat in the cerebral and cardiac vessels but remains unchanged in the vessels of the splanchnic region and extremities.

Of obvious significance in distribution of the blood supply between the various vascular regions is not only their liberation from vasoconstrictor impulses but local hemodynamic regulation of the blood supply of the individual organs. This is proved by the fact that a decrease in the vasoconstrictor tone by the gangliolytics in those vascular regions where it is most pronounced does not always cause their blood supply to increase.

It is evident from the foregoing data that the blood supply of the various organs under the influence of ganglion-blocking agents is a fairly complicated subject, one that requires detailed study. For example, there can be no doubt that the complex chain of processes set in motion by these drugs primarily affects the cardiac circulation. The state of the myocardial blood supply is particularly important because impairment of the coronary circulation is generally associated with hypertension, which is often treated with these drugs. But the available experimental and clinical data are not systematic.

It is difficult to get a clear idea about the effect of the substances on the myocardial blood supply from the scattered references in the literature. For example, Acheson and Moe (1945) found that tetraethylammonium improved cardiac efficiency in the heart-lung preparation, but in experiments on intact animals it produced EKG changes indicative of a deterioration of the blood supply and reflected in compression of the S-T segment. According to Hill and coauthors (1949), administration of tetraethylammonium to dogs with the cardiac blood supply impaired by ligation of the left coronary artery had no significant effect on the condition of the animals and EKG dynamics.

Hexamethonium has been more thoroughly studied in this respect. Murphy et al. (Murphy, O'Brien, Rennie, Capps, Rowe and Crumpton, 1953) investigated its effect on the volume rate of the coronary flow, cardiac output, and myocardial oxygen consumption in normal dogs and dogs with experimental hypertension. They found that the coronary flow and cardiac output were somewhat reduced by hexamethonium, but myocardial oxygen consumption scarcely changed. Under the conditions of hypertension, the results were similar to these except that hypertension induced by the drug was more pronounced.

However, according to Crumpton et al. (1954), hexamethonium increased the coronary flow but decreased the resistance of the cardiac vessels. A. A. Belous and G. O. Magakyan (1957) used hexamethonium to treat coronary insufficiency in monkeys. They found that the drug improved the EKG data and the animals' general condition.

There is also some information on mecamylamine. Rowe et al. (Rowe, Castillo, Maxwell, White, Freeman and Crumpton, 1958) found that mecamylamine in doses of 0.5-1 mg/kg reduced the volume rate of the coronary flow, the effect being accompanied by gradually increasing hypotension. Myocardial oxygen consumption and cardiac output did not change. Calculation of coronary resistance from these experiments showed that it was increased by the administration of mecamylamine.

Ganglerone (1,2-dimethyl-3-diethylaminopropyl p-isobutoxybenzoate hydrochloride) was another ganglion-blocking agent investigated. According to R. A. Aleksanyan (1959), the drug has a beneficial effect on the coronary circulation by increasing the volume rate of the blood flow.

It is evident from this brief review of the literature that the results of experimental investigations dealing with the effect of ganglion-blocking agents on the coronary circulation are quite contradictory. Equally ambiguous and varied are the materials on the effectiveness of gangliolytics against coronary disorders.

Some authors report on the favorable results obtained by using tetraethylammonium (TEA) for coronary circulatory disorders. For example, Christy (1949) noted that it greatly helped patients with coronary insufficiency and improved the EKG indices when used over a period of a year. Lyons et al. (Lyons, Moe, Neligh, Hoobler, et al., 1947) found that the drug markedly relieved pain in coronary thrombosis. Ye. V. Erine (1958) states that hexamethonium is beneficial for patients with hypertension.

The drug has also been found helpful in improving the EKG of patients with hypertension accompanied by cardiac insufficiency (Schroeder, 1952; Moyer, Miller and Ford, 1953; Sieber, Grimson and Orgain, 1953; Wyman et al., 1953). However, there are also reports that the use of gangliolytics may cause cardiac complications. For example, Judson, Hollander, et al. (1956) found that the administration of hexamethonium and pentolinium sometimes produced angina pectoris in persons with coronary disease. The authors think that these complications were due to a sharp drop in blood pressure and resultant insufficiency of the cardiac blood supply.

Lindgren and Frisk (1948) studied the effect of TEA on the EKG and general condition of patients with coronary atherosclerosis. They found that it caused a marked deterioration in their condition along with anginal attacks.

It is evident from the foregoing data that ganglion-blocking agents have been little investigated in the respect of interest to us. It is impossible to get any clear idea from them on the nature of the effects of the group as a whole on the coronary circulation or on the mechanism of action of the individual drugs.

We decided to investigate five of these agents--nicotine, tetraethylammonium, hexamethonium, pentamine and mecamylamine. Since nicotine has some unusual characteristics (two-phase action on the autonomic ganglia and unsuitability for clinical use), it is described in a special section. We performed two series of experiments, recording in one changes in the volume rate of the coronary flow under the influence of these drugs and recording, in the other, the resistance of the cardiac vessels.

1. Nicotine

Nicotine is rightly called the classical ganglion-blocking agent. Langley's discovery (Langley and Dickinson, 1889) of the ganglion-blocking properties of nicotine initiated research on substances capable of interfering with the transmission of excitation in the autonomic ganglia. Nicotine is not used in the clinic because its blocking action on the ganglia, manifested only when administered in large doses, is preceded by a pronounced phase of excitation of the n-cholinoreactive structures. Moreover, it has highly diverse effects on different systems of the organism, another factor that militates against its clinical use.

The influence of nicotine on the myocardial blood supply is of interest in two respects. First, changes in resistance of the coronary vessels produced by nicotine are useful, owing to its diphase effect on the ganglia, in judging the mechanism of action of ganglion-blocking agents on the cardiac vessels. Secondly, there is the very practical matter of the role of smoking in the origin and clinical symptoms of angina pectoris.

It is a well known fact that smoking stimulates attacks in patients with angina pectoris (Moschowitz, 1928; White and Scharder, 1934; others). Bryant and Wood (1947) found that smoking by such persons may bring on attacks during which there are EKG changes reflecting diminished amplitude of the T wave and occurrence of ventricular extrasystoles. These changes are characteristic of an impaired myocardial blood supply. Several authors investigated smoking as a test for determining functional impairment of the coronary circulation. For example, H. Mandelbaum and R. Mandelbaum (1952), Henderson (1953) and Davis et al. (1956) found that smoking can be used to detect circulatory disorders on the ballistocardiogram when other tests are negative.

There have been a great many studies dealing with the effect of nicotine on the cardiovascular system. Intravenous injection of the substance produces hypertension, the mechanism of action of which is still obscure. It is difficult to say whether the elevation of blood pressure is due solely to excitation of the ganglia because the introduction of nicotine into the body creates conditions that may indirectly promote the development of hypertension, e.g., intensified secretion of epinephrine by the adrenals, resulting in a higher level of the hormone in the circulating blood (Van Slyke and Lawson, 1950; Beauvallet and Fugazza, 1956; Kiser, Booher and Watts, 1958).

Nicotine's action on the vasomotor center may also play a part in the development of hypertension. Some investigators found that it has a direct

vasoconstrictor effect. For example, Haimovici and Pick (1946) and Haimovici (1948) showed in experiments on the preparation of an isolated vascular bed in the frog leg that nicotine constricts the blood vessels even after the ganglia are blocked by tetraethylammonium. However, it was later discovered that this effect is due to the fact that norepinephrine is released from the chromaffin cells embedded in vascular tissues (Kottegoda, 1953; Burn, Leach, Rand and Thompson, 1959). Nicotine induces very sharp changes in cardiac activity. The bradycardia that immediately follows its administration as a result of excitation of the parasympathetic ganglia and vagus nerve center gives way to tachycardia and then arrhythmia.

According to the many investigators who studied the effect of nicotine on cardiac activity, the nature of the resultant EKG changes suggests the onset of myocardial hypoxia (Von Ahn, 1954; Kelli et al., 1954; Kien, Lasker and Scherrod, 1958; others). Experimental data confirm the numerous clinical observations whereby the pain that arises in the heart during smoking is caused by the EKG changes characteristic of impaired coronary circulation (Cornwall, 1934; Bryant and Wood, 1947; H. Mandelbaum and R. Mandelbaum, 1952; Russek, Zohman and Dorset, 1955).

Thus, EKG observations indicate that nicotine impairs the myocardial blood supply apparently by constricting the coronary vessels. However, in recording the volume rate of the blood flow in the cardiac vessels, most investigators noted a perceptible increase following the administration of nicotine (Mansfeld and Hecht, 1933; Dietrich and Schimert, 1939; Schmitthenner, Reigel and Hafkenschiel, 1956). Constriction of the coronary vessels under the influence of nicotine was observed only by those investigators who performed experiments on the isolated heart (Meyer, 1912; Morawitz and Zahn, 1914; Romm and Kuschnir, 1928).

Kien, Lasker and Scherrod (1958) studied the mechanism of action of nicotine on the myocardial blood supply. They found that the drug increased the rate of blood flow because of hypertension and intensified cardiac output. In the experiments in which hypertension was not pronounced, the coronary flow remained more or less unaffected. However, myocardial oxygen consumption did not rise in all the experiments in which cardiac activity increased. In fact, in some instances there was a temporary decrease in oxygen consumption immediately after the drug was used. Since the development of EKG changes indicative of deterioration in the cardiac blood supply coincided with decreased myocardial oxygen consumption, the authors believe that the phenomenon was due to the coronary circulatory disorders produced by nicotine. This view was supported by Levy et al. (Levy, Mathers, Mueller and Nickerson, 1947), who showed that after the administration of nicotine there is no correlation between the intensity of EKG changes and increase in cardiac activity.

Numerous experimental and clinical observations were concerned with comparing changes in the coronary circulation induced by nicotine in healthy animals and in animals with an impaired cardiac blood supply (due to atherosclerosis, myocardial infarct, etc.). For example, Rinzler et al. (Rinzler, Travell, Karp and Charlson, 1956) observed that the drainage of blood from the coronary vessels decreased under the influence of nicotine in rabbits with

experimental atherosclerosis. In healthy animals, on the other hand, drainage increased. Bellet et al. (Bellet, Kersbaum, Mead and Schwartz, 1941) found that EKG changes occurred in animals with experimental myocardial infarct after the administration of nicotine in doses one-quarter those given to normal animals.

The clinical data are similar (Henderson, 1953; Simon, Iglauer and Braunstein, 1954; others). According to Bargeron, Ehmke, Conlubol, et al. (1957), smoking by healthy human beings increases the coronary blood flow, but does not affect myocardial oxygen consumption. The authors think that coronary vasoconstriction follows the administration of nicotine only if the coronary circulation is already impaired.

It is evident that the published data dealing with the effect of nicotine on the coronary circulation are abundant but conflicting. One thing is clear: nicotine is capable of impairing the myocardial blood supply. However, the underlying mechanism of action and the factors responsible for the difference in the intensity of its action on blood vessels under normal and pathological conditions are still obscure. Most investigators are inclined to believe that the main reason for impairment of the coronary circulation is myocardial hypoxia. It has been assumed a priori that nicotine can constrict the coronary vessels, but there is no experimental proof of this as yet.

Our observations showed that intravenous injection of nicotine causes a pronounced increase in the coronary flow accompanied by hypertension (table 7). In a dose of 0.1 mg/kg, the drug increased the blood flow by 83 ± 21 percent on the average (5 experiments). It is evident from the figures that the changes in blood flow were quite variable. This was true, but to a lesser degree, for blood pressure changes. Injection of the same dose of nicotine resulted in blood pressure rising 54 ± 3.8 percent above the original level. It is interesting to note that in a dose of 1 mg/kg (i.e., 10 times the amount) nicotine failed to induce more pronounced changes in the volume rate of the coronary flow. The intensity of the flow in the experiments increased 81 ± 21 percent, while blood pressure rose somewhat more than after a 0.1 mg/kg dose, i.e., 85 ± 4.1 percent. However, the difference in these effects was statistically insignificant ($p = 0.1$). There was no correlation between the changes in coronary blood flow and blood pressure.

The sharp fluctuations in rate of coronary flow in the different experiments and the lack of correlation with changes in blood pressure make it impossible to get a definite idea about the state of cardiovascular tone after the administration of nicotine from the data obtained by recording the coronary flow. The changes in hemodynamic conditions mask the true effect of nicotine on the coronary vessels.

Clearer results were obtained in experiments with resistography (table 8). Nicotine in a dose of 1 mg/kg increased the resistance of the coronary vessels 16 ± 6.1 percent on the average (in 6 experiments).

Blood pressure meanwhile rose 68 ± 7.8 percent above the original level (fig. 16). The cardiac vessels became constricted 10-16 sec after nicotine was

TABLE 7. EFFECT OF NICOTINE ON THE VOLUME RATE OF THE CORONARY FLOW AND ON BLOOD PRESSURE. (MEAN DATA IN PERCENTAGES OF THE ORIGINAL LEVEL WITH THE STANDARD ERROR)

Agent	Dose in mg/kg	No. of experiment	Changes in outflow in percentages of the original level	Mean data	Changes in blood pressure in percentages of the original level	Mean data
Nicotine	0.1	1	+ 39		+41	
		2	+120		+61	
		3	+149	+83 ± 21	+59	+54 ± 3.8
		4	+ 68		+62	
		5	+ 37		+48	
Nicotine	1	1	+ 24		+68	
		2	+ 32		+87	
		3	+160	+81 ± 21	+82	+85 ± 4.1
		4	+ 35		+98	
		5	+106		+99	
		6	+138		+67	
		7	+ 80		+93	

TABLE 8. EFFECT OF NICOTINE ON RESISTANCE OF THE CORONARY VESSELS AND ON BLOOD PRESSURE. (MEAN DATA IN PERCENTAGES OF THE ORIGINAL LEVEL WITH THE STANDARD ERROR)

Agent	Dose in mg/kg	No. of experiment	Changes in resistance in percentages of the original level	Mean data	Changes in blood pressure in percentages of the original level	Mean data
Nicotine	0.1	1	+12		+ 39	
		2	+46		+161	
		3	+20	+16 ± 6.1	+ 54	+68 ± 7.8
		4	-10		- 41 + 57	
		5	+14		+44	
		6	+ 7		+71	
Nicotine[1]	1	1	+13 - 9		+110 - 16	
		2	+15 - 5	+16 ± 2.7	+ 75 - 32	+86 ± 8.7
		3	+24 - 4	- 6 ± 1	+ 89 - 40	-29 ± 4
		4	+12 - 7		+ 71 - 29	

[1]The + sign designates the increased resistance phase of the vessels; the - sign designates the decreased resistance phase.

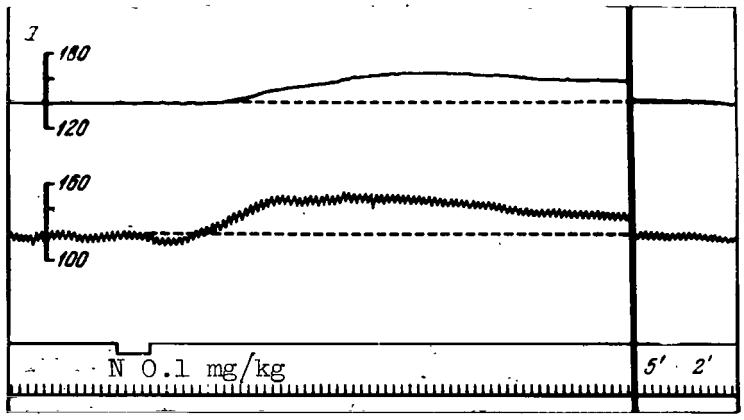


Figure 16. Effect of nicotine (0.1 mg/kg on resistance of the coronary vessels and on blood pressure. Top to bottom: perfusion pressure (resistogram), blood pressure, mark of administration of the agent, time mark--5 sec. a--background and administration of nicotine; b--5 min after administration of nicotine.

injected, the effect lasting 5-6 min. It is interesting to note that the time the vasoconstrictor effect developed coincided with the start of EKG changes.

Injection of 1 mg/kg of nicotine caused changes of diphase character in resistance of the coronary vessels. Just as in the preceding series of experiments, resistance increased immediately after the drug was injected, but the intensity did not exceed that which followed the 0.1 mg/kg dose. The increase averaged 16 ± 2.7 percent (in 4 experiments). In 4-6 min vasoconstriction gave way to vasodilation. The latter phase was less intense than the former (averaging 6 ± 1 percent).

Changes in blood pressure after injection of 1 mg/kg of nicotine were likewise diphase. Elevation of blood pressure, averaging 86 ± 8.7 percent, was followed by a lowering (averaging 29 ± 4 percent in 4 experiments).

Analysis of the experiments with nicotine seemed to indicate that the increase in resistance of the cardiac vessels after administration of 0.1 mg/kg of the drug is due to the fact that it excites the autonomic ganglia. The effect is two-phase if the dose is increased, a decrease in resistance following the initial increase. We decided to verify this by administering nicotine following the action of tetraethylammonium (5 mg/kg). The experiments revealed that within 5-6 min of injecting TEA, i.e., with the transmission of excitation blocked in the ganglia, the administration of nicotine did not cause the resistance of the coronary vessels to increase (fig. 17). Thus, vasoconstriction under the influence of nicotine is the result of its exciting action on the autonomic ganglia. Additional confirmation came from the observations of G. F. Kareva (1961), who found that TEA prevented EKG changes following the administration of nicotine.

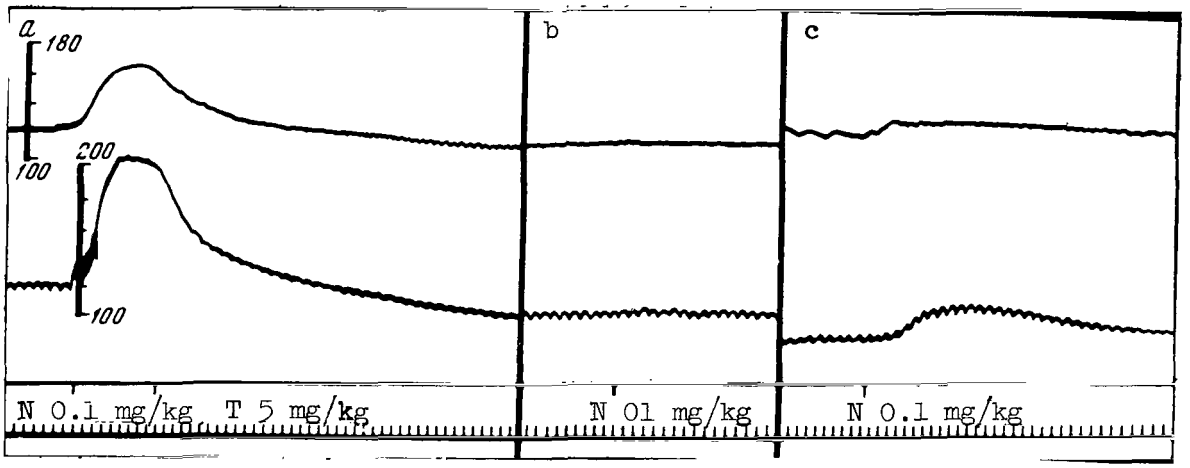


Figure 17. Effect of nicotine (0.1 mg/kg) on resistance of the coronary vessels and on blood pressure following a blockade of transmission of excitation in the autonomic ganglia by tetraethylammonium (5 mg/kg). Top to bottom: perfusion pressure (resistogram), blood pressure, mark of administration of the agent, time mark--5 sec. a--elimination of the effect of nicotine by tetraethylammonium; b--second administration of nicotine 6 min after tetraethylammonium; c--start of restoration (25 min after administration of tetraethylammonium).

It is interesting to note that nicotine in a dose of 0.1 mg/kg apparently causes maximum excitation of the autonomic ganglia responsible for conduction of excitation to the cardiac vessels because a 10-fold increase in the dose does not intensify the constriction phase of the cardiac vessels (table 8). However, in this dose nicotine is not potent enough to achieve a distinct ganglion-blocking effect because the cardiac vessels respond to the drug only by constricting. The ganglion-blocking effect is fully manifested when used in a dose of 1 mg/kg in the form of decreased resistance of the cardiac vessels, i.e., dilatation.

A comparison of the results of our experiments with nicotine, performed with the aid of two different methods (recording of the blood flow rate and resistography), throws some light on the differences in action of nicotine on the myocardial blood supply under normal and pathological conditions of the heart and coronary vessels. The nicotine-induced vasoconstriction in the healthy organism is compensated by sharp changes in hemodynamics. Despite the increased vascular coronary tone, the volume of blood passing through the vessels in a unit of time may grow owing to elevation of arterial pressure. In this event the heart receives enough oxygen and myocardial hypoxia does not occur.

In atherosclerosis or other conditions that impair myocardial nutrition, disruption of the mechanisms that regulate blood circulation may prevent

nicotine-induced vasoconstriction from being compensated by the hemodynamic factors, thereby intensifying the changes in the myocardial blood supply. These changes have much in common with the changes brought about by epinephrine. However, epinephrine distinctly dilates the coronary vessels after constricting them and it influences myocardial metabolism, an effect that nicotine does not have. This may be the reason that nicotine impairs the coronary circulation so rapidly.

Our observations on nicotine, derived from a comparison of changes in the rate of coronary flow, cardiovascular resistance, and blood pressure may not embrace all the aspects of its mechanism of action on the myocardial blood supply, but they do throw some new light on the problem.

2. Other Ganglion-Blocking Agents (Tetraethylammonium, Hexamethonium, Pentamine and Mecamylamine)

The first series of experiments involved recording the volume rate of blood flow in the cardiac vessels. They showed that the gangliolytics cause different changes in this index. For example, tetraethylammonium (TEA) had the most pronounced capacity to increase the volume rate of the coronary flow. A slight increase (8-10 percent above the original level) often followed even the use of low doses (1-2 mg/kg), but the effect was greatest with doses of 3-5 mg/kg. A 5 mg/kg dose increased the blood flow on the average 36 ± 2.9 percent above the original level (fig. 18) in 5 experiments, the effect lasting 5-10 min. Experiments with resistography showed that the same doses of TEA decreased the resistance of the coronary vessels. Statistical processing of the results revealed that the decrease in resistance after a dose of 5 mg/kg averaged 10 ± 4 percent of the original level (in 7 experiments). Blood pressure, meanwhile, dropped 29 ± 3.6 percent. It is evident from the data summarized in table 9 that the degree of change in blood flow and blood pressure under the influence of tetraethylammonium ranged within fairly broad limits.

The results varied most in the experiments with hexamethonium. In low doses (0.25 mg/kg) this drug generally decreased the volume rate of the blood flow 9 ± 3 percent on the average (in 6 experiments), i.e., fluctuations were pronounced. Blood pressure in the same experiments was lowered 21 ● 4.7 percent. Much larger doses of the drug (1-2 mg/kg) produced even sharper fluctuations. In some cases it decreased the volume rate of the coronary flow, while in others it increased the outflow of blood from the coronary sinus. A comparison of the changes in blood flow with the original values showed that the blood flow rate decreased when it was originally quite high (usually more than 6 ml/min), whereas it increased in the experiments with low original values (fig. 19). Thus, the effect of hexamethonium varies from case to case, depending on the myocardial blood supply.

In the experiments involving recording of the resistance of the coronary vessels, hexamethonium generally reduced it. For example, the drug (2 mg/kg) reduced resistance in 6 out of 8 experiments and increased it in only 2.

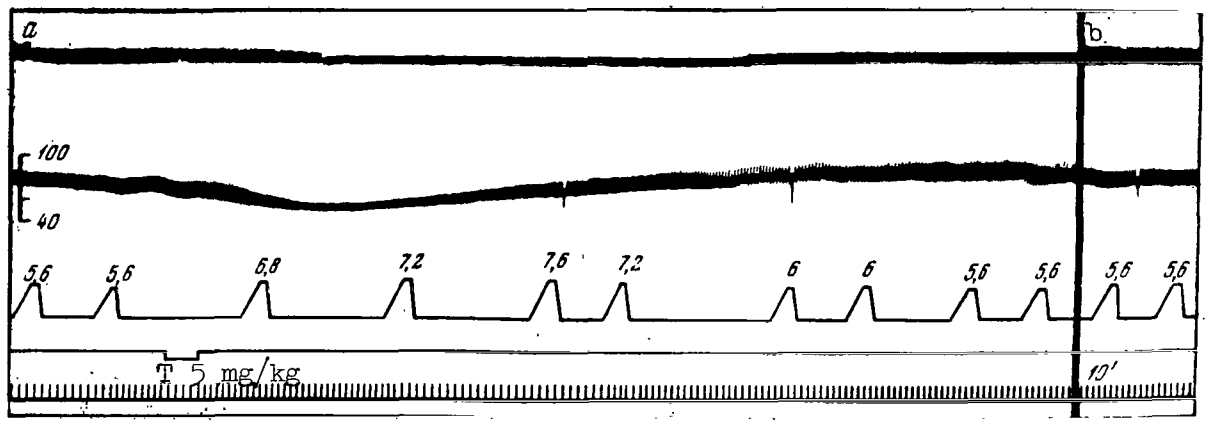


Figure 18. Effect of tetraethylammonium (5 mg/kg) on the volume rate of the coronary flow, amplitude of cardiac contractions and blood pressure.
Top to bottom: amplitude of cardiac contractions (recording by means of a myocardiograph with pneumatic transmission), blood pressure, volume rate of coronary flow (peak of columns--value of blood flow for 15 sec, figures above the columns--minute volume of coronary flow). In the kymograms presented below of the experiments with recording of the volume rate of coronary flow, the peak of the columns shows the value of the blood flow in 15 sec; the figures above the columns--minute volume of coronary flow, mark of administration of the agent, time mark--5 sec.

TABLE 9. EFFECT OF GANGLION-BLOCKING AGENTS ON THE VOLUME RATE OF THE CORONARY FLOW, RESISTANCE OF THE CORONARY VESSELS AND BLOOD PRESSURE. (MEAN DATA IN PERCENTAGES OF THE ORIGINAL LEVEL WITH THE STANDARD ERROR)

Agent	Dose in mg/kg	Change in volume rate of coronary flow	Change in resistance of coronary vessels	Change in blood pressure	Remarks
Tetraethyl-ammonium	5	+36 ± 2.9	-10 ± 4	-29 ± 3.6	The results of the experiments with hexamethonium and pentamine were processed by groups, depending on the nature of the effect (see text). The + sign designates the mean increase in volume rate of the coronary flow; the - sign designates a decrease therein.
Hexamethonium	2	+38 ± 4.7 -30 ± 2.8	- 8 ± 3.2	-28 ± 9.1	
Pentamine	2	+34 ± 7.5 -31 ± 8.9	-10 ± 5.1	-23 ± 4.4	
Mecamylamine	0.5	-27 ± 5.2	+ 5 ± 2.6	-32 ± 6.7	

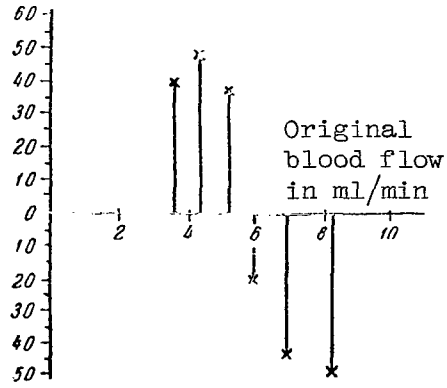


Figure 19. Relationship between changes in the coronary blood flow and its original values under the influence of 2 mg/kg of hexamethonium.
Ordinate: from 0 upward--values of the maximum increase in blood flow in percentages of the original level; from 0 downward--values of the maximum decrease in volume rate of coronary blood flow in percentages of the original level. Abscissa: original--original values of the volume rate of coronary blood flow in ml/min.

Processing of the data revealed that the resistance of the coronary vessels increased when the creation of normal myocardial blood supply conditions required the use of a perfusion pump to maintain a high rate of blood flow to the cardiac vessels. When the flow rate was average or low, resistance under the influence of hexamethonium decreased. Thus, the experiments with resistography confirmed our earlier observation that there is a relationship between the effect of hexamethonium and the original myocardial blood supply conditions.

Statistical processing of the results of the experiments with resistography indicated, according to the mean values, that the effect of hexamethonium should be interpreted as a reduction of coronary vascular resistance. A 2 mg/kg dose reduced resistance 8 ± 3.2 percent on the average (in 8 experiments). Blood pressure in these experiments was 28 ± 9.1 percent below the original level (table 9). Like tetraethylammonium, hexamethonium tended to decrease the amplitude of cardiac contractions.

Like hexamethonium, pentamine (methylaminodiethylene bis ethyldimethyl ammonium bromide) produced changes in the volume rate of the coronary flow. Injected intravenously in doses of 0.2-0.25 mg/kg, it generally reduced the volume rate 14 ± 5.2 percent on the average (in 6 experiments). Its variable effect was especially pronounced when used in large doses. In these experiments, as in those with hexamethonium, the amount of blood flowing out of the coronary sinus was more or less related to the original level. With a fairly rapid blood supply to the myocardium (original value of outflow--10 to 12 ml/min), the administration of pentamine reduced the volume rate of the coronary flow. With a slow blood supply, pentamine tended to increase the volume rate. The effect of the drug administered in the above doses persisted 15-25 min.

In most experiments pentamine decreased the resistance of the coronary vessels. Resistance increased only when the myocardial blood supply conditions made it necessary to create a high rate of blood flow with a perfusion pump. Statistical processing of the results of the experiments involving the administration of 2 mg/kg of pentamine showed that, according to the mean values, a reduction of resistance was the most probable effect. It averaged 10 ± 5.1 percent below the original level (mean data of 6 experiments). Blood pressure in the same experiments dropped 23 ± 4.1 percent, with a marked decrease in the amplitude of cardiac contractions.

The most pronounced decrease in volume rate of the coronary flow was noted in the experiments with mecamylamine. This drug reduced the blood flow in every one of the experiments. Processing the data of this series of experiments revealed that the drug reduced the blood flow even in low doses (0.1-0.5 mg/kg). The effect grew with increase in the dose. After a dose of 2 mg/kg the decrease averaged 27 ± 5.2 percent (in 5 experiments). Mecamylamine also induced a gradual but prolonged drop in blood pressure. Within 5-7 min of administration, the latter dropped on the average 18 ± 0.7 percent below the original level (in 5 experiments). And it did not always return to the original values. One of the experiments with mecamylamine is shown in figure 20.

In the experiments with resistography, we found that mecamylamine had little effect on the resistance of the cardiac vessels. In 4 out of 6 experiments when the drug was administered in a 0.5 mg/kg dose, resistance increased. Statistical processing of the results of this series showed that the increase amounted to +5 ± 2.6 percent of the original level. It is evident from the figures that the effect was quite variable. Like the other ganglion-blocking agents, mecamylamine slightly decreased the amplitude of cardiac contractions.

Table 9 summarizes the results of two series of experiments on the effect of ganglion-blocking agents on the volume rate of the coronary flow and on resistance of the coronary vessels. It is evident from the table that these agents, with the exception of mecamylamine, decrease the resistance of the coronary vessels. But in doing so they significantly alter the level of systemic arterial pressure. A comparison of the results of these experiments with the

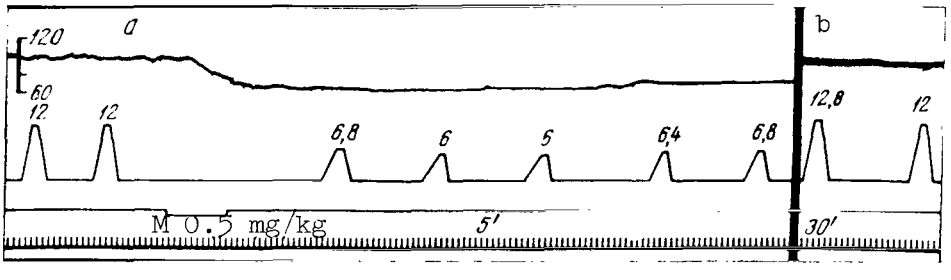


Figure 20. Effect of mecamylamine (0.5 mg/kg) on the volume rate of the coronary flow.
Top to bottom: blood pressure, volume rate, mark of administration of the agent, time mark--5 sec. a--Background and administration of mecamylamine; b--30 min after administration.

data obtained by recording the volume rate of the coronary flow shows that fluctuations in resistance of the cardiac vessels play a definite role, but they are not the dominant factor in those changes in the myocardial blood supply which occur in response to the administration of ganglion-blocking agents.

These agents are known to have no significant effect on the intensity of myocardial metabolism (Murphy, Brien, Rennie, Capps, Rowe and Crumpton, 1953; Rowe, Castillo, Maxwell, White, Freeman and Crumpton, 1958). It would seem, therefore, that hemodynamic factors are of major significance in the changes in myocardial blood supply observed after the action of ganglion-blocking agents.

Inasmuch as ganglion-blocking agents reduce the cardiac output at the same time that they promote hypotension (Gilmore, Kopelman, et al., 1952; Murphy et al., 1953; Crumpton et al., 1954; Wakim, 1955; Scott, Kaplan, et al., 1956; Rowe, Castillo, Maxwell, et al., 1958), an analysis of their effect on the myocardial blood supply should take into account the fact that the nature and intensity of the effect depends in each case on the relationship between the ensuing changes in the general hemodynamics and resistance of the cardiac vessels. Judging by the results of our experiments, the most favorable conditions for the myocardial blood supply are created by the administration of tetraethylammonium, for this drug invariably increases the volume rate of the coronary flow by reducing the resistance of the cardiac vessels. Mecamylamine adversely affects the blood supply because it considerably decreases the volume rate of the coronary flow, thereby increasing in most cases the resistance of the coronary vessels.

Note that among the agents under study only mecamylamine increased the resistance of the cardiac vessels in the majority of experiments. This may be due to the fact that mecamylamine has a peripheral vasoconstrictor action, as demonstrated by Yu. V. Uranov (1958), who observed that mecamylamine markedly constricted the vessels of the isolated heart.

The differences we observed in the cardiovascular responses to hexamethonium and pentamine in relation to the original values of the coronary flow are of considerable interest. There is still no convincing explanation of these facts. The intensity of the hypotension induced by ganglion-blocking agents is known to vary with the original tone of the vasoconstrictor nerves (Page, 1949; Paton and Zaimis, 1952). This circumstance may also be significant for the cardiovascular system as well.

Our findings may likewise be of value in evaluating the role of vasoconstrictor innervation in coronary vascular tone. According to recent ideas, vasoconstrictor impulses are transmitted to the coronary vessels along the sympathetic nerves. The vagus nerve is not directly involved in the innervation of the coronary vessels (Denison and Green, 1958; Szentivanyi and Nagy, 1959; H. Wang, Blumental and S. Wang, 1960). It follows, then, that the effect of ganglion-blocking agents on the resistance of the coronary vessels depends on a blockade of the sympathetic ganglia which transmit excitation to the cardiac vessels. The results of our investigations show that gangliolytics do not substantially reduce the resistance of the cardiac vessels, the maximum decrease

being 10 percent of the original level (experiments with tetraethylammonium and pentamine). It would seem, therefore, that under normal conditions the cardiac vessels do not possess marked vasoconstrictor tone. This view is in line with that of a number of investigators who studied nervous regulation of the blood circulation in different vascular beds (Green and Kepchar, 1959; V. M. Khayutin, 1960).

In summary, tetraethylammonium is the most consistent of ganglion-blocking agents in increasing the myocardial blood supply by accelerating the volume rate of the coronary flow and reducing the resistance of the coronary vessels. If the myocardial blood supply is low, hexamethonium and pentamine increase the rate of coronary flow. Under certain conditions, however, they may impair the blood supply. Mecamylamine decreases the volume rate of the coronary flow and in most instances intensifies the resistance of the cardiac vessels. The drug has an adverse effect on the myocardial blood supply. Our experimental data are in agreement with clinical observations in which the use of gangliolytics brought on or increased the frequency of anginal attacks. Thus, we believe that the results of our investigations should be considered when selecting ganglion-blocking agents for the treatment of hypertension accompanied by impairment of the coronary circulation.

Comparatively small doses of nicotine increase coronary vascular tone. If the dose is raised, nicotine has a diphase effect, with vasoconstriction giving way to vasodilation. This pattern of changes in resistance of the coronary vessels is due to the diphase action of nicotine on the autonomic ganglia. Since nicotine raises blood pressure sharply, the increase in coronary vascular resistance does not always cause the myocardial blood supply to deteriorate. An elevation of aortic pressure helps to increase the volume rate of the coronary flow. However, when the coronary circulation is impaired, hemodynamic regulation may be inadequate and nicotine-induced vasoconstriction will have an adverse effect on the myocardial blood supply. This view is confirmed by clinical observations in which smoking increased the frequency of anginal attacks in patients with coronary insufficiency.

CHAPTER 4. EFFECT OF ANALGESICS ON THE CORONARY CIRCULATION

Analgesics are widely used in the treatment of coronary insufficiency to relieve the pain associated with anginal attacks. It is extremely important, therefore, to determine what changes these agents bring about in the myocardial blood supply. It is necessary to know, above all, whether they are capable of dilating the cardiac vessels. There are some published reports on morphine. For example, Kountz (1932) observed in experiments on the isolated surviving human heart that morphine increases the outflow from the coronary vessels. This was the conclusion of Elek and Katz (1942) who studied the isolated fibrillated heart. Macht (1915) and Rössler (1930) investigated the effect of morphine on the coronary flow in the heart-lung preparation. They found that morphine increased the outflow from the cardiac vessels.

According to Mautner and Pick (1929), who studied the effect of morphine on the coronary circulation under the conditions of experimental spasm of the coronary vessels induced by pituitrin, morphine injected intravenously into dogs, cats and rabbits delayed the onset of the spasm for more than an hour. On the other hand, Van Egmond (1911) and Wegria (1951) showed that morphine has no significant effect on the coronary flow. Pettus, Geiger and Grzebien (1942) found that intravenous injection of morphine in therapeutic doses did not impair the EKG in human beings. They concluded that the narcotic is useful in cases of acute coronary circulatory disorders. Similarly, Papper and Brandley (1942) observed that morphine in therapeutic doses did not significantly alter the cardiac rate, cardiac output, or blood pressure level in human beings.

The effect of morphine on blood pressure has been more thoroughly studied. We shall briefly review the literature because it is valuable in appraising the effect of morphine on the blood supply of various organs, the heart in particular.

Morphine is known to cause hypotension. This effect, however, is irregular and variable in intensity and duration because several mechanisms are involved. For example, according to Schmidt and Livingston (1953), the mechanism of vasodilatation under the influence of morphine is due to its direct action on the capillaries and to depression of the vasomotor center. According to Evans, Nasmyth and Stewart (1952), the lowering of blood pressure following intravenous infusion of morphine is due both to its effect on the vasomotor center and to its ability to stimulate the release of histamine. This is also the conclusion of Feldberg and Paton (1951).

Compared with morphine, there are few references in the literature to the effect of other analgesics on the coronary circulation. According to several authors, methadon and demerol have spasmolytic properties. However, they were

manifested mainly in experiments on isolated organs (decrease in spastic contractions of isolated segments of the intestine, vasodilatation in the isolated ear of rabbits, etc.) (Scott and Chen, 1946; Kirchhof and Uchiyama, 1947). In intact animals demerol and methadon increased the tone of uterine and intestinal smooth muscle tone (Scott, Kohlstaedt, Robbins and Israel, 1947; Uchiyama, Kirchhof and David, 1947; M. D. Mashkovskiy and R. I. Kruglikova-L'vova, 1950; B. I. Legostev and M. K. Sozina, 1950; M. D. Mashkovskiy and V. I. Ishchenko, 1952; B. I. Legostev, 1952).

Thus, the question of whether the above analgesics possess spasmolytic properties is still moot. However, judging by some clinical observations, they are successfully used in several diseases for both their pain-relieving and spasmolytic effects (Kirchhof and David, 1948; Troxil, 1948; Popkin, 1948; V. M. Karatygin and Z. I. Rozhnova, 1953; S. V. Bazanova, 1954; K. B. Radugin, 1954; I. V. Sokolov, 1955; others).

We investigated four analgesics--morphine, demerol, methadon and thecodeine (hydroxycodeine hydrochloride)--injected intravenously. Morphine was found to increase the volume rate of the coronary flow. In a 1 mg/kg dose it increased the rate 25 ± 3.7 percent (mean data of 8 experiments). One of these experiments is shown in figure 21a. Blood pressure after this dose of morphine dropped insignificantly. In some experiments blood pressure did not change at all, and the maximum decrease was no more than 8 percent below the original level. The drop in blood pressure after the above dose averaged 3 ± 1.1 percent (mean data of 8 experiments). When the dose was boosted to 2 mg/kg, the rate of the coronary flow rose slightly (to 30-35 percent).

The effect, which lasted 12-15 minutes, developed after a marked drop in blood pressure (25-30 percent below the original value). Experiments with perfusion of the coronary vessels showed that morphine distinctly lowers perfusion pressure, a sign of reduced resistance of the vessels to the flow of blood (fig. 21b). Statistical processing of this series of experiments revealed that the resistance of the coronary vessels was reduced by morphine (2 mg/kg) 13 ± 1.3 percent (mean data of 8 experiments). Blood pressure in the same experiments dropped 32 ± 5.8 percent. Thus, our experiments show that morphine has a favorable effect on the blood circulation. The resultant increase in the myocardial blood supply is apparently due to the fact that it reduces the resistance of the coronary vessels.

The results were quite different in the experiments with demerol. In doses of 1-3 mg/kg this analgesic significantly decreased the volume rate of the coronary flow. After a 1 mg/kg dose, the rate slowed on the average 15 ± 4.8 percent (in 5 experiments). This effect developed under the conditions of low blood pressure which, however, was no more than 25 percent of the original value, averaging 13 ± 3.7 percent. Increasing the dose to 3 mg/kg resulted in the coronary flow rate slowing 40-45 percent (fig. 22a). This dose sometimes lowered blood pressure considerably (about 30-35 percent).

The decrease in rate of blood flow is presumably not a sign of vasoconstriction. It merely indicates that when blood pressure is low, less blood flows through the cardiac vessels in a unit of time. However, the experiments

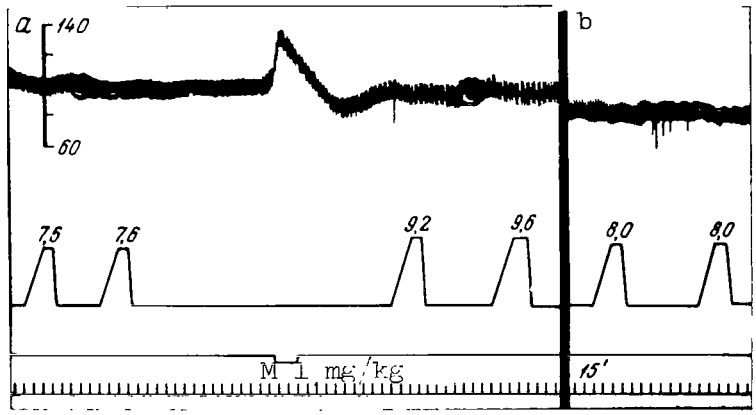


Figure 21a. Effect of morphine (1 mg/kg) on the volume rate of the coronary flow.
Top to bottom: blood pressure, volume rate of coronary flow, mark of administration of the agent, time mark--5 sec.
a--background and administration of morphine; b--after 15 min.

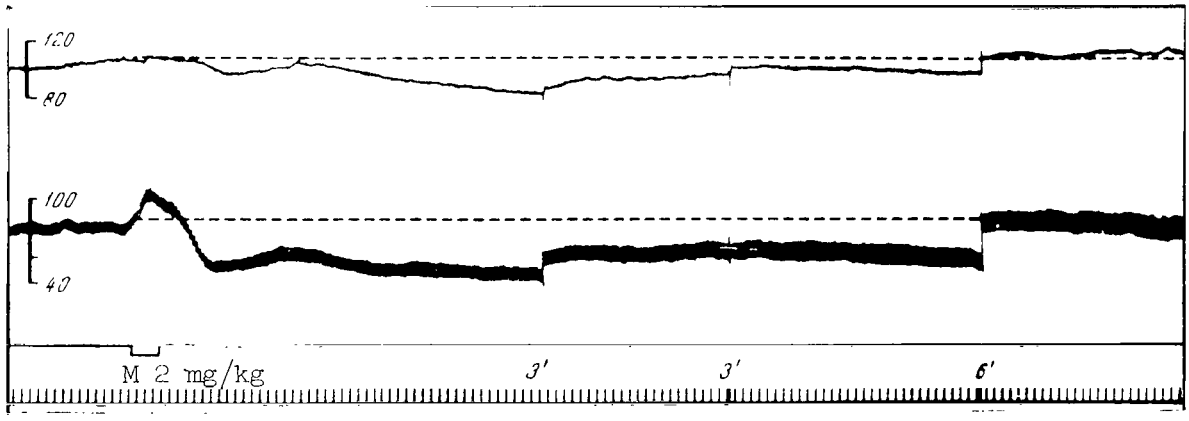


Figure 21b. Effect of morphine (2 mg/kg) on resistance of the coronary vessels and on blood pressure.
Top to bottom: perfusion pressure (resistogram), blood pressure, mark of administration of the agent, time mark--5 sec (time the kymograph was halted--3, 3 and 6 min).

with resistography show that under the influence of demerol the resistance of the coronary vessels generally increases (fig. 22b). Following the administration of a 1 mg/kg dose, the increase in vascular resistance averaged 6 ± 1.6 percent (in 9 experiments).

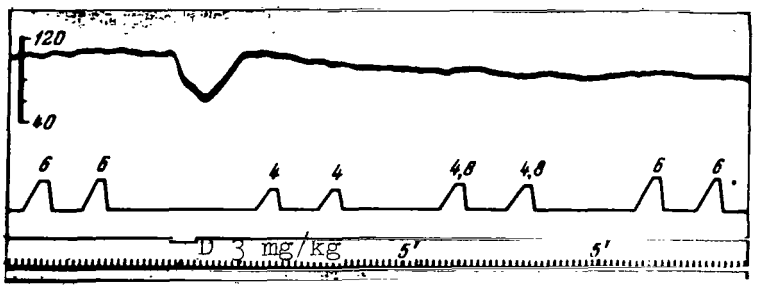


Figure 22a. Effect of demerol (3 mg/kg) on the volume rate of the coronary flow.
Top to bottom: blood pressure, volume rate of coronary flow, mark of administration of the agent, time mark--5 sec (time the kymograph was halted--5 min).

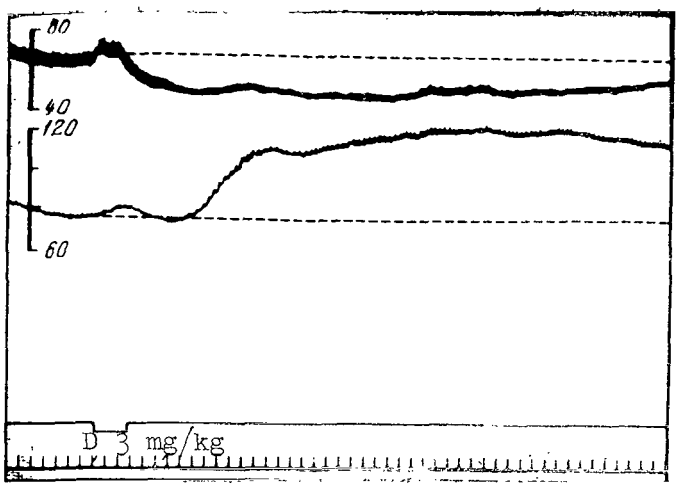


Figure 22b. Effect of demerol (3 mg/kg) on resistance of the coronary vessels.
Top to bottom: blood pressure, perfusion pressure (resistogram), mark of administration of the agent, time mark--5 sec. Broken lines--original level of blood and perfusion pressures.

Methadon, like demerol, sharply decreases the volume rate of the coronary flow. A 1 mg/kg dose decreased the blood flow in the cardiac vessels 37 ± 4.3 percent (mean data of 8 experiments). This effect occurred in the absence of hypotension. Blood pressure meanwhile usually dropped no more than 20 percent below the original level (8 ± 2.5 percent on the average). The effect of methadon lasted 15-25 minutes. But the resistance of the coronary vessels changed much less under the influence of methadon than did the volume rate of the coronary flow. The changes were rather vague. In some cases resistance increased 9-10 percent above the original level, while in others it slightly decreased.

Statistical processing of the results of the experiments in which 1 mg/kg doses of the drug were used revealed that resistance of the coronary vessels averaged +4 ± 2.8 percent (in 5 experiments), i.e., it scarcely changed.

The results of the experiments with thecodeine were about the same. The volume rate of blood flow in the cardiac vessels decreased 15-20 percent after administration of 1-3 mg/kg doses, while the average rate of blood flow decreased 14 ± 4.3 percent (in 6 experiments). It is evident from the figures that changes in the blood flow varied considerably from experiment to experiment. In some cases there was no decrease in the volume rate of blood flow in the cardiac vessels, while in others it was quite pronounced. Blood pressure was little affected; it dropped slightly in most cases, averaging 8 ± 2.5 percent (in 8 experiments) after a 1 mg/kg dose. Thecodeine caused the resistance of the coronary vessels to fluctuate slightly and transiently. Statistical processing of the data of 6 experiments showed that changes in the resistance of the coronary vessels after the administration of a 2 mg/kg dose averaged 2 ± 3.3 percent, i.e., their resistance scarcely changed.

The data obtained in the experiments with analgesics are summarized in tables 10 and 11.

TABLE 10. EFFECT OF ANALGESICS ON THE VOLUME RATE OF THE CORONARY FLOW AND ON BLOOD PRESSURE. (MEAN DATA IN PERCENTAGES OF THE ORIGINAL VALUES WITH THE STANDARD ERROR)

Agent	Dose in mg/kg	No. of experiments	Change in volume rate of coronary flow	Change in blood pressure
Morphine	1	8	+25 ± 3.7	- 3 ± 1.1
Demerol	1	5	-15 ± 4.8	-13 ± 3.7
Thecodeine	1	6	-14 ± 4.3	-12 ± 1.9
Methadon	1	8	-37 ± 4.3	- 8 ± 2.5

TABLE 11. EFFECT OF ANALGESICS ON RESISTANCE OF THE CORONARY VESSELS AND ON BLOOD PRESSURE. (MEAN DATA IN PERCENTAGES OF THE ORIGINAL VALUES WITH THE STANDARD ERROR)

Agent	Dose in mg/kg	No. of experiments	Change in resistance	Change in blood pressure
Morphine	2	8	-13 ± 1.3	-32 ± 5.8
Demerol	1	9	+ 6 ± 1.6	-21 ± 4.5
Thecodeine	1	5	+ 4 ± 2.8	-15 ± 5
Methadon	2	6	- 2 ± 3.3	-11 ± 5.6

A comparison of the figures reflecting the effect of each of the analgesics investigated on the volume rate of the coronary flow, resistance of the cardiac vessels, and blood pressure shows that the increase in myocardial blood supply caused by morphine results from a decrease in resistance of the coronary vessels, i.e., from their dilatation. Demerol, on the other hand, decreases the volume rate of blood flow in the cardiac vessels by increasing their tone.

Thus, the changes in myocardial blood supply under the influence of morphine and demerol may be related to their direct effect on the tone of the cardiac vessels. Methadon and thecodeine greatly decrease the rate of blood flow in the cardiac vessels without significantly affecting the tone of the coronary vessels. Moreover, the decrease in rate of coronary flow produced by these agents cannot be ascribed to hemodynamic factors because they failed to bring about any significant changes in the level of systemic arterial pressure. The decrease in volume rate of the coronary flow may be the result of the bradycardia induced by the analgesics. This assumption, however, requires experimental proof.

Our experiments showed that morphine alone is capable of increasing the cardiac blood supply. Demerol, methadon, and thecodeine decrease the volume rate of the coronary flow and, as a result, may adversely affect the cardiac blood supply. Judging by the results of our experiments, morphine would seem to be the most useful of the analgesics for acute impairment of the coronary circulation. Consequently, we thought it worthwhile to study this drug in greater detail. We performed a special series of experiments to investigate its effect on myocardial oxygen consumption, using the photoelectric method, which is based on measurement of the amount of oxyhemoglobin in venous blood draining from the coronary sinus. Ye. M. Kreps' oxyhemometer was used for continuous measurement. A plexiglas cuvette was inserted into the pickup of the instrument. It was connected on one side to a catheter through which the blood flowed from the coronary sinus and on the other, to the jugular vein through a rubber tube. Thus, the oxyhemoglobin content of the venous coronary blood was determined at the same time that the volume rate of the coronary flow was being recorded. The scale of the instrument was enlarged and regraduated. The method is described in more detail by I. Ye. Kisin (1959). The oxyhemoglobin content of the venous coronary blood obtained by this method was used to calculate the amount of oxygen consumed by the myocardium. The following formula was used:

$$A = \frac{1.34\ (C_1 - C_2)\ V \cdot H}{100},$$

where A is the amount of oxygen in ml/min; C_1 is the oxyhemoglobin content of arterial blood in percentages (determined with a reflecting oxyhemometer; with artificial respiration--regularly with a possible error of +5 percent); C_2 is the oxyhemoglobin content in percentages of the blood flowing out of the coronary sinus; V is the volume rate of the coronary outflow in ml/min; H is the amount of hemoglobin in 1 ml of blood in grams. The hemoglobin content was determined with a photoelectric erythrohemometer.

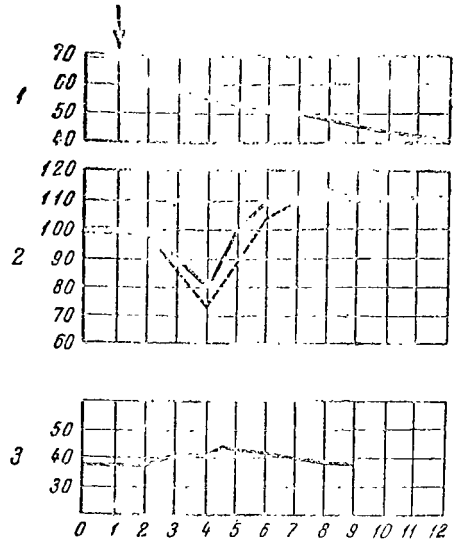


Figure 23. Effect of morphine (1.5 mg/kg) on the cardiac blood supply.
1--Arterial pressure in mm Hg; 2--volume rate of coronary flow in percentages of the original level (unbroken line) and myocardial consumption of oxygen from blood drained by the coronary sinuses (broken line) in percentages of the original level; 3-- amount of oxygen in coronary sinus blood in percentages of oxyhemoglobin. Abscissa--time in minutes.

The experiments showed that changes in volume rate of the coronary flow and myocardial oxygen consumption occurred simultaneously under the influence of morphine (fig. 23). An increase in the former was accompanied by an increase in the latter. However, in some of the experiments the volume rate of the coronary flow increased a little more than did the myocardial oxygen consumption.

The cardiac output is little changed by morphine, although it may occasionally diminish (Hürthle, 1890; Gruber and Robinson, 1929; Hamilton, Moore, Kinsman and Spurling, 1932; Resnik, Friedeman and Harrison, 1935; Papper and Brandley, 1942).

Thus, morphine creates the same situation as some other vasodilators (papaverine, the purines, etc.), i.e., the myocardial blood supply grows in the absence of increased activity by the heart. Such a situation would be favorable for the blood supply of an ailing heart if the amount of oxygen consumed by the myocardium did not increase equally with acceleration of the coronary blood flow. We still do not know whether the myocardium receives additional blood at this time, nor do we know the mechanism of the positive effect of the vasodilator agents which simultaneously increase myocardial oxygen consumption. However, the clinical effectiveness of this group of drugs is well known. Therefore, by analogy with other agents (possessing similar action on the coronary

circulation) used to treat angina pectoris, it is reasonable to believe that the use of morphine should give good results. Moreover, the ability of morphine to dilate the coronary vessels, as revealed in our experiments, is particularly valuable when combined with its analgesic properties.

This conclusion applies only to morphine. The effectiveness of the other analgesics (thecodeine, methadon, and demerol) in the treatment of angina pectoris, judging by our investigations, cannot be attributed to their direct influence on the cardiac vessels.

CHAPTER 5. EFFECT OF PHENOTHIAZINE DERIVATIVES ON THE CORONARY CIRCULATION

The most interesting of the many manifestations of the pharmacological action of the phenothiazine derivatives are their spasmolytic properties, particularly their capacity to dilate the blood vessels. Attention has been focused largely on chlorpromazine, a typical representative of this group of compounds. Chlorpromazine lowers blood pressure considerably (Heinecker, 1954; Huidobro, 1954; M. D. Mashkovskiy, S. S. Liberman and A. I. Polezhayeva, 1955; Spitzbarth et al., 1955; others). The numerous investigations of the mechanism of hypotension that develops after the administration of chlorpromazine indicate that the main cause is a reduction of peripheral vascular resistance (Foster, O'Mullane, Gaskell, Churchill and Davidson, 1954; Kopera and Amitage, 1954; Spurr, Horvath and Farrand, 1956; Duff, McIntyre and Butter, 1956; others). This is due mainly to the drug's spasmolytic action and to its ability to block the peripheral adrenergic structures. A number of investigators sought to determine what significance its effect on the central nervous system has in the development of the vasodilator effect. For example, Foster et al. (1954) and Ginsburg and Duff (1956) believe that vasodilatation caused by chlorpromazine is due to combined central and peripheral action. They drew this conclusion from experiments with plethysmographic recording of vascular tone in the extremities. They found that intravenous injection of the drug has a more potent vasodilator effect than intraarterial injection (directly into the vessels of the extremities).

Several authors who studied the mechanism of the vasodilator effect of chlorpromazine (in experiments with cross perfusion of various isolated vascular regions retaining only a nerve connection with the organism) found that the vessels became dilated only when the drug was injected directly into the vessels of the isolated region (injection into the donor or into the perfusion stream). It had no vasodilator effect when injected intravenously into the recipient (Decourt, 1954; Kovach, Kleinsorge, Roheim, Iranyi and Rosner, 1957; Yu. I. Vikhlyayev, 1960). These observations show that it is the peripheral, sympatholytic, and myotropic action of chlorpromazine that plays the decisive role in producing the hypotensive effect and thus decreasing vascular tone. The sympatholytic mechanism of the vasodilator action of the drug is presumably responsible for the difference in intensity of the changes that it causes in the blood supply of the various vascular regions. The original tone of the vessels apparently determines the intensity of the vasodilator effect.

The literature dealing with the effect of chlorpromazine on the blood circulation confirms this view. The vasodilator effect is particularly sharp in the vessels of the extremities, the vasomotor component of which is quite pronounced (Green and Kepcher, 1959; V. M. Khayutin, 1960). Pickering and Ahlquist (1955) used a rotameter to record the blood flow in the femoral and renal arteries of

dogs and found that chlorpromazine in a 1 mg/kg dose increased the blood flow in the extremities considerably, but had little effect on the blood flow in the kidneys. This was also the finding of Shackman et al. (Shackman, Wood-Schmidt, Graber, Melrose and Lynn, 1954), who calculated the intensity of circulation in human extremities from plethysmographic changes. They observed that intravenous injection of the drug sharply increased the blood flow in the extremities.

Arens and Witzleb (1955) used the thermoelectric method of recording the blood flow and found that chlorpromazine accelerated the blood flow in the carotid, mesenteric, splenic, and renal arteries as soon as it was injected, the amount of increase varying from vessel to vessel. The cerebral blood vessels are known to lack a distinct neurogenic tone (Green and Kepcher, 1959). This is obviously the reason why chlorpromazine cannot dilate these vessels, but it does tend to decrease blood flow. Moyer, Morris et al. (1956), for example, showed that chlorpromazine in low doses, which do not sharply lower blood pressure, slightly decreases the volume rate of the cerebral blood flow. However, under the conditions of marked hypotension, this effect may be considerably intensified. The administration of norepinephrine restores the original blood pressure level, thereby overcoming a chlorpromazine-induced decrease in blood flow in the cerebral vessels. Thus, blood flow changes in the cerebral vessels under the influence of chlorpromazine are due to hemodynamic conditions, which play a major role in regulating the cerebral blood circulation. This was also the conclusion of others who studied the subject (Finnerty, Witkin and Fazekas, 1954; Fazekas, Albert and Alman, 1955).

There is no detailed information in the literature on the effect of chlorpromazine on the coronary circulation. The few available studies mostly involved the use of the isolated heart preparation. Courvoisier et al. (Courvoisier, Fournel, Ducrot, Kolsky and Koetschet, 1953) in experiments with perfusion of an isolated (by Langendorf's method) heart found that chlorpromazine increased drainage from the cardiac vessels when it was added to the perfusate in high concentrations. At the same time it decreased the amplitude of cardiac contractions. Similarly, Melville (1954) observed an increase in drainage from the coronary vessels during perfusion of an isolated rabbit heart only when chlorpromazine was used in high concentrations, which resulted in marked inhibition of cardiac activity.

Witzleb and Budde (1955) found in experiments with the heart-lung preparation that large doses of chlorpromazine (5-20 mg/kg) resulted in a slight increase in the coronary flow without affecting the cardiac output or rate. In the case of the heart in situ, the drug, according to these same authors, was less potent. However, this sort of comparison is scarcely acceptable because the authors used larger doses in experiments with the heart-lung preparation than in those with the heart in situ.

The most detailed information is found in the work of Maxwell et al. (Maxwell, Rowe, Castillo, Schuster, White and Crumpton, 1958), who investigated the effect of chlorpromazine on several hemodynamic indices in experiments on dogs. They found that the drug did not significantly change the volume rate of the coronary flow. The phase blood flow decreased slightly as a result of the increase in cardiac rate. According to these authors, chlorpromazine likewise

failed to change the cardiac output and only slightly increased myocardial oxygen consumption. Since these effects developed under the conditions of hypotension, calculation of the peripheral resistance of the coronary vessels showed that it decreased slightly.

Some authors found that chlorpromazine had a positive effect on EKG changes in experimental myocardial infarct (Szabo, Solti, Rev, Refi and Maguesi, 1957; Szabo, 1959; S. Ya. Kaplun and Ye. G. Kopteva, 1960). This was also the conclusion of Cahn, Melon and Dubrasquet (1953) and Cahn and Melon (1954), who found that the use of a lytic cocktail consisting of chlorpromazine, promethazine, and meperidine favorably affected the course of experimental infarct induced in dogs by ligating the descending branch of the left coronary artery.

Despite the indistinct vasodilator effect of chlorpromazine on the coronary vessels under experimental conditions, some authors reported success in using the drug to relieve cardiac pain in functional disorders of the coronary circulation. According to Argelander (1954), the daily administration of 75-300 mg reduced pain considerably and improved the condition of patients with symptoms of coronary insufficiency. Petzold and Huth (1954) treated angina pectoris with sleep therapy, chlorpromazine, and promethazine, which relieved coronary spasms for a long time.

According to some clinical reports, chlorpromazine and combinations thereof with other phenothiazine derivatives and analgesics are effective against myocardial infarct, for they relieve pain and improve the patients' general condition. In some instances they normalize the EKG (Heinecker, 1954; Duening, 1954; Roisin et al., 1954; Broustet, Bricand, et al., 1955; A. A. Krivchik, 1957; P. L. Sukhanin and V. P. Chuchkalov, 1958).

Thus, the clinical observations on the use of chlorpromazine for disorders of the coronary circulation are not always consistent with the experimental material. This inconsistency may be due to the fact that the relatively meager published data were mostly derived from the isolated heart preparation. The beneficial effect of chlorpromazine in circulatory disorders is possibly the result of its neuroplegic action.

A much more potent spasmolytic and vasodilator agent, judging by the literature, is mepazine (pacatal). Possessing less hypotensive action than chlorpromazine, it increases the volume rate of the blood flow in the vessels of the intestine, spleen, kidneys, and extremities. Its vasodilator effect is immediate but transient (Arens and Witzleb, 1955). The data on its effect on the cardiac vessels are contradictory. Nieschulz, Popendiker and Sack (1954) found that the drug dilated only slightly the vessels of the rabbit heart in the Langendorf preparation, whereas Cahn and Melon (1954) found that it distinctly increased the outflow from the vessels of the isolated heart. Kopt' (1955) and Witzleb and Budde (1955) also noted marked cardiac vascular dilatation induced by the drug in the heart-lung preparation.

As demonstrated by Nieschulz, Popendiker and Hoffman (1955), mepazine can prevent coronary spasms in rats induced by pituitrin. Thus, the effect of this drug on the coronary vessels is most evident in experiments on intact animals

subjected to experimental impairment of the coronary circulation. This is confirmed by clinical findings that mepazine reduces pain caused by coronary spasm (Kleinsorge and Rösner, 1956; Broglie and Jorgensen, 1954; Bockel, 1955; Broglie, Jorgensen and Voss, 1956).

The literature we cited characterize chlorpromazine and mepazine as agents capable of acting favorably on the blood circulation in various vascular regions and of improving the myocardial blood supply. However, the meager experimental data and, in some cases, their disagreement with clinical observations require a more detailed investigation of the effect of these drugs on the coronary circulation. This led us to undertake a comparative study of several phenothiazine derivatives. To obtain an idea of the changes they produce in the myocardial blood supply, we used a variety of experimental procedures: recording of the volume rate of the coronary flow and resistance of the coronary vessels to the flow, study of the capacity of these compounds to prevent or relieve experimental coronary spasms induced by pituitrin. The last series included acute and chronic experiments. In the acute experiments we evaluated their capacity to terminate pituitrin-induced (2 U/kg) coronary spasms. We judged changes in the myocardial blood supply from changes in the volume rate of the blood flow. Pituitrin sharply reduced the drainage of blood from the coronary sinus of cats. The substances were administered while pituitrin was manifesting its greatest effect, i.e., at the height of the spasm. In the chronic experiments on cats and rats, we studied the ability of the drugs to prevent pituitrin spasms of the coronary vessels, evaluating the changes in myocardial blood supply from the EKG changes. The method of inducing a pituitrin spasm was described in detail above (p. 32).

1. Chlorpromazine and Mepazine

The experiments showed that a 1 mg/kg dose of chlorpromazine slightly increased the volume rate of the coronary flow above the original level (by 13-15 percent). Blood pressure meanwhile dropped 30-35 percent and remained at this very low level for 1 to 1-1/2 hours after the drug was administered. A 2 mg/kg dose of chlorpromazine increased the effect to 20-30 percent. Statistical processing of the results of these experiments revealed that the 2 mg/kg dose increased the volume rate of the coronary flow 22 ± 5.6 percent (average of 6 experiments) (fig. 24). The increase in blood flow was accompanied, however, by a sharp drop in blood pressure (64 ± 6.4 percent in the same experiments) and decrease in amplitude of cardiac contractions. The effect lasted about 1-1/2 hours. The 2 mg/kg dose was optimum because a further increase not only did not intensify the effect, it sometimes even reduced the outflow of blood from the coronary sinus. This effect developed under the conditions of marked hypotension.

The experiments in which the effect of chlorpromazine on the resistance of the coronary vessels was investigated, showed that a 2 mg/kg dose markedly decreased (by 40 ± 8 percent) the tone of the cardiac vessels while sharply lowering blood pressure.

Table 12 presents data illustrating the effect of chlorpromazine on the volume rate of the coronary flow, resistance of the cardiac vessels, and blood

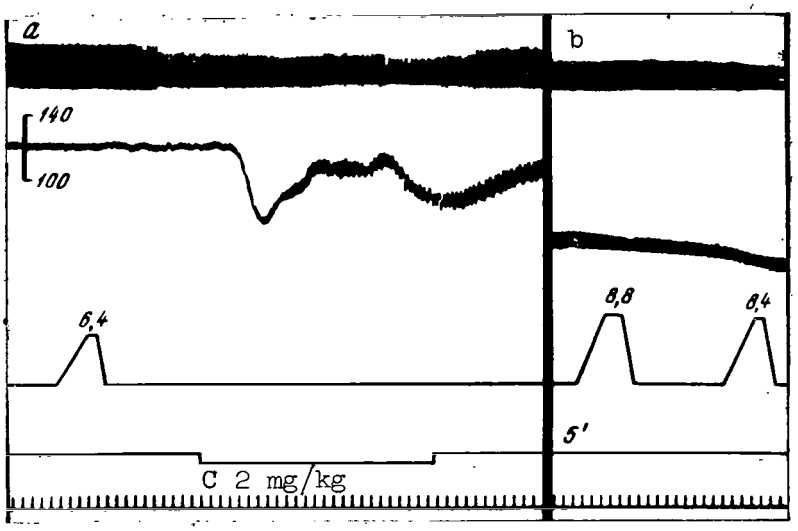


Figure 24. Effect of chlorpromazine (2 mg/kg) on the volume rate of the coronary flow, blood pressure, and amplitude of cardiac contractions.
Top to bottom: amplitude of cardiac contractions, blood pressure, volume rate of coronary flow, mark of administration of the agent, time mark--5 sec. a--background and administration of the agent; b--5 min after administration.

pressure. A comparison of the mean figures reflecting the changes in these values after administration of the drug shows that it markedly dilated the cardiac vessels (and lowered their resistance to the blood flow). However, vasodilatation in other regions produced severe hypotension, resulting in a slight increase in the volume of blood passing through the cardiac vessels in a unit of time, despite the dilatation of the cardiac vessels. When the dose of chlorpromazine was increased, hypotension intensified and instead of the expected growth in the myocardial blood supply, the opposite often happened, i.e., the blood flow in the coronary vessels diminished. Our assumption that chlorpromazine might be more effective during spasm of the coronary vessels was borne out by experiments. A 2 mg/kg dose of chlorpromazine injected at the time of maximum decrease in outflow of blood from the coronary sinus actually increased it. However, the spasm was not completely relieved. The volume rate of the coror ry flow was restored to only 75-80 percent of the original level. When the dose was raised to 3 mg/kg, the drug's effectiveness did not increase, apparently because of the sharp drop in blood pressure and decrease in amplitude of cardiac contractions observed under these conditions.

Mepazine proved to be much more active against the cardiac blood supply. A 2 mg/kg dose increased the volume rate of the coronary flow 30-40 percent while slightly lowering the blood pressure (20-25 percent below the original level). Increasing the dose to 5 mg/kg intensified the effect. Statistical processing of the results of these experiments showed that the mean increase in volume rate of the blood flow after a 5 mg/kg dose of mepazine was 58 ± 5.9 percent. Blood pressure in the same experiments dropped 25 ± 2.3 percent below the original level. The effect persisted 70-90 min.

TABLE 12. EFFECT OF PHENOTHIAZINE DERIVATIVES (CHLORPROMAZINE, MEPAZINE, AND CHLORACIZIN) ON THE VOLUME RATE OF THE CORONARY FLOW, RESISTANCE OF THE CORONARY VESSELS TO THE BLOOD FLOW, AND BLOOD PRESSURE. (MEAN DATA IN PERCENTAGES OF THE ORIGINAL LEVEL WITH THE STANDARD ERROR)

Agent	Dose in mg/kg	Mean values of change in blood flow	Confidence limits	Mean values of change in resistance	Confidence limits	Mean values of change in blood pressure	Confidence limits
Chlorpromazine	2	+22 ± 5.6	6.4- 37.6	-40 ± 8	18-62	-64 ± 64	46.3-81.7
Mepazine	5	+58 ± 5.9	44.7- 71.3	-18 ± 1	15.7-20.2	-25 ± 2.3	19.8-30.2
Chloracizin	5	+90 ± 9.2	70.5-109.5	-41 ± 4.6	30.2-52.8	+ 4 ± 2.2	-0.6 ± 8.6

The resistance of the coronary vessels diminished under the influence of mepazine. The effect was not very pronounced because resistance of the cardiac vessels after a 5 mg/kg dose dropped 18 ± 1 percent (mean data of 10 experiments). A comparison of the mepazine-induced changes in the rate of the coronary flow, resistance of the coronary vessels, and blood pressure revealed that, despite indistinct dilatation of the cardiac vessels, the conditions of the myocardial blood supply were improved by the administration of mepazine (table 12).

Mepazine was even more effective during a pituitrin-induced spasm of the cardiac vessels. When injected at the time of maximum decrease in the coronary flow induced by pituitrin, mepazine (5 mg/kg) not only completely relieved the spasm of the cardiac vessels, but sometimes slightly increased the outflow of blood from the coronary sinus above the original level (fig. 25).

Mepazine proved to be equally effective when tested on a model of pituitrin spasm of the coronary vessels induced in a chronic experiment. When injected intravenously (2 U/kg) into cats and rats, it generally produced the EKG changes characteristic of an impaired myocardial blood supply: changes in position of the S-T segment relative to the isoelectric line, change in the shape and size of the T wave, and, finally, disruption of the cardiac rhythm due to myocardial hypoxia. Three days after conclusion of the control experiment with the administration of pituitrin alone, the same animals received mepazine 3-5 min before pituitrin. A control experiment was performed 2 or 3 days later. Judging by the EKG data, preliminary injection of mepazine prevented coronary spasm. It either failed to develop at all or was much weaker than in the control. The effectiveness of mepazine against pituitrin spasm was far greater

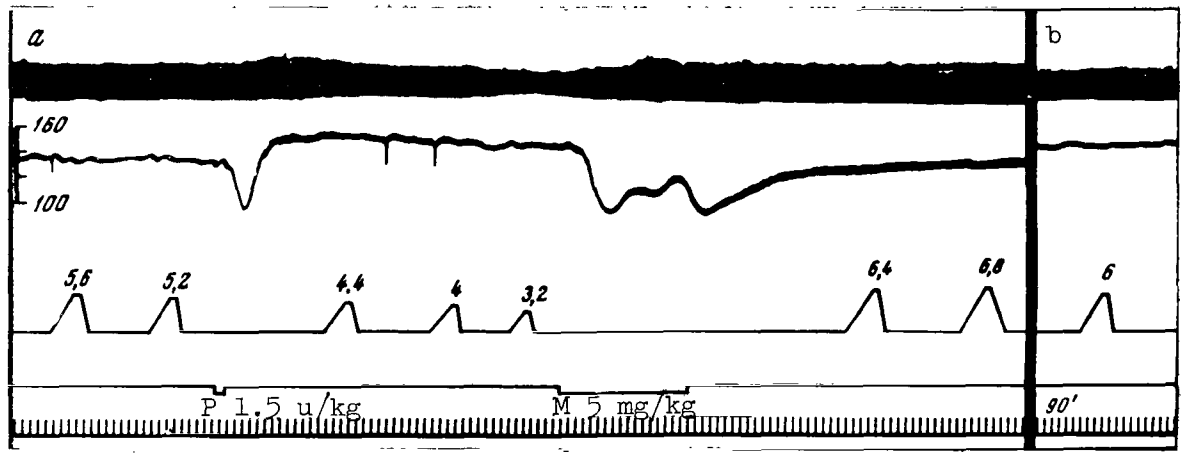


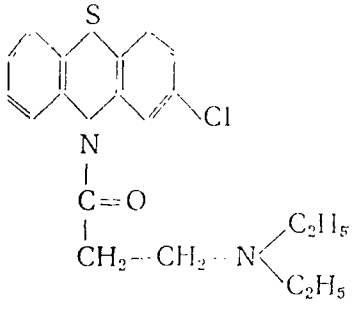
Figure 25. Effect of mepazine (5 mg/kg) on the volume rate of the coronary flow, blood pressure, and amplitude of cardiac contractions during spasm of the coronary vessels induced by pituitrin (unit/kg).
Top to bottom: amplitude of cardiac contractions, blood pressure, volume rate of coronary flow, mark of administration of the agent, time mark--5 sec. a--background and administration of the agent; b--90 min after administration.

than that of chlorpromazine, which prevented arrhythmia, but not the EKG changes indicative of an insufficiency of the myocardial blood supply.

Thus, our investigations showed that mepazine is capable of increasing the myocardial blood supply and, as such, seems to be a promising agent for the treatment of disorders of the coronary circulation.

2. Chloracizin

Investigations on the relationship between the chemical structure and pharmacological action of several phenothiazine derivatives showed that the substitution of dialkylaminoacyl radicals in the side chain for dialkylaminoalkyl radicals intensifies their spasmolytic properties (Yu. I. Vikhlyayev, 1958; Dahlbom and Ekstrand, 1951). In the Institute of Pharmacology and Chemotherapy of the USSR Academy of Medical Sciences, S. V. Zhuravlev and A. N. Gritsenko (1956) synthesized several dialkylaminoacyl phenothiazine derivatives. During the search for new and effective vasodilator agents we studied the activity of these compounds as agents capable of increasing the cardiac blood supply. Perhaps the most active of these compounds on the cardiac vessels was 10 (β-diethylaminopropionyl)-2-chlorophenothiazine - chloracizin.



Our experiments showed that chloracizin can increase the cardiac blood supply. Even after doses of 2-2.5 mg/kg, the volume rate of the coronary flow increased 70-75 percent, and after a 5 mg/kg dose it increased 100 percent or more above the original level (fig. 26a). Statistical processing of the results of the experiments revealed that the 5 mg/kg dose increased the outflow of blood from the coronary sinus 90 ± 9.2 percent on the average (in 17 experiments). Blood pressure usually dropped 20-25 percent immediately after the drug was administered, but 2-3 min later it returned to normal or a little above. The effect of chloracizin on the cardiac vessels lasted 60-70 min on the average.

The resistance of the cardiac vessels decreased sharply under the influence of chloracizin. In a 2 mg/kg dose it reduced resistance 28 ± 2 percent and in a 5 mg/kg dose, 41 ± 4.6 percent below the original level (mean data of 7 experiments) (fig. 26b).

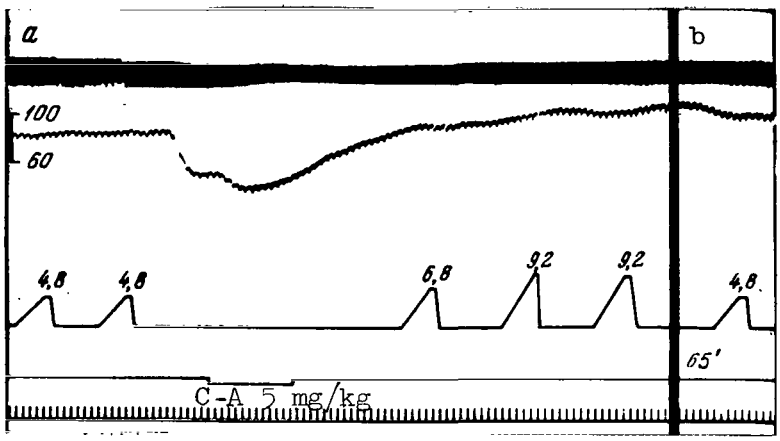


Figure 26a. Effect of chloracizin (5 mg/kg) on the volume rate of the coronary flow, blood pressure, and amplitude of cardiac contractions.
Top to bottom: amplitude of cardiac contractions, blood pressure, volume rate of coronary flow, mark of administration of the agent, time mark--5 sec. a--background and administration of chloracizin; b--65 min after administration.

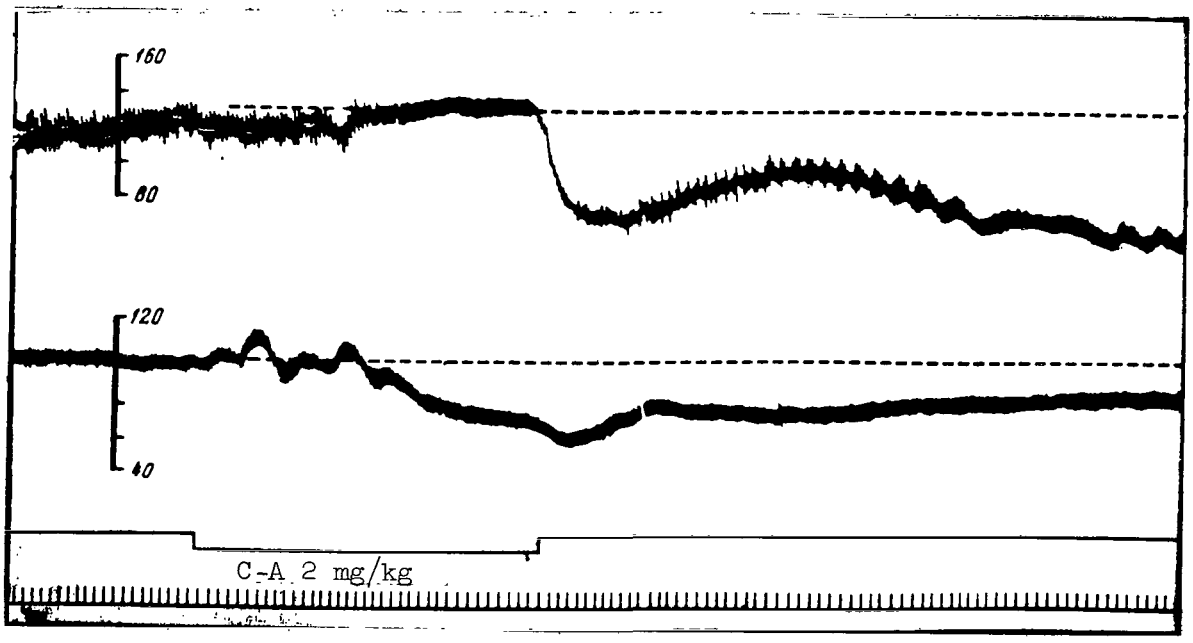


Figure 26b. Effect of chloracizin (2 mg/kg) on resistance of the coronary vessels.
Top to bottom: perfusion pressure (resistogram), blood pressure, mark of administration of the agent, time mark--5 sec.

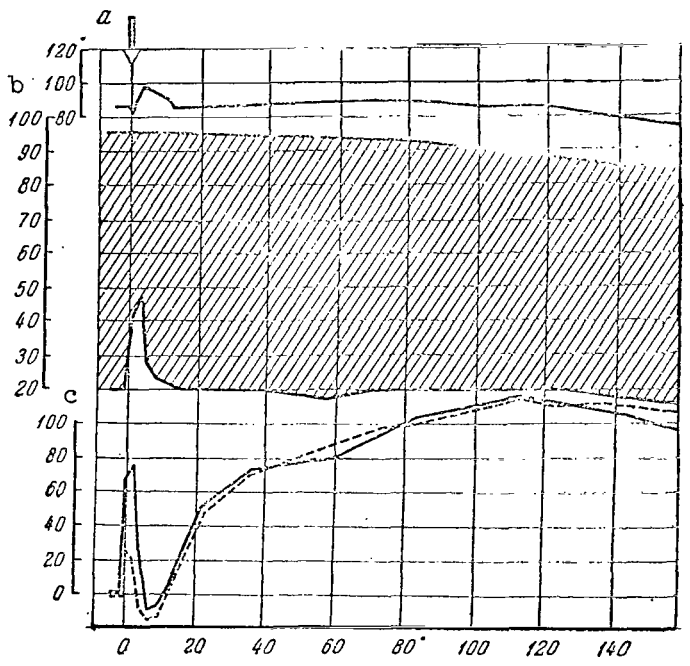


Figure 29. Effect of chloracizin (5 mg/kg) on the volume rate of the coronary flow and on myocardial oxygen consumption. Ordinate: a--arterial pressure in mm Hg; b--oxygen content of arterial blood and coronary sinus blood, in percentages; c--solid line: volume rate of coronary flow in percentages of the original level; broken line: cardiac consumption of oxygen from blood drained by the coronary sinus, in percentages of the original level. Abscissa: time in minutes.

Cardiac output was studied in chronic experiments on dogs using Grollman's acetylene method (1932) in Khrenov's modification (1946). The method is based on the principles of Fick and Bornstein. According to Fick, the cardiac output is calculated from experimentally derived values of the arteriovenous difference and minute oxygen consumption. Fick's formula:

$$\text{cardiac output} = \frac{\text{oxygen consumption in 1 min}}{\text{arteriovenous oxygen difference}} .$$

The idea of inhaling indifferent gases to determine the arteriovenous difference was conceived by Bornstein. Grollman's method in Khrenov's modification involves a mean error of 20 percent and is inferior in this respect to Fick's method. However, it does not require catheterization of the pulmonary artery, securing of the animal, and anesthesia, as Fick's method does, and it permits dynamic investigation of the cardiac output many times in the same animal.

Study of the cardiac output by this method consists of the following steps: (1) determination of gas exchange, (2) inhalation of a gas mixture consisting of 8-10 percent acetylene and 20 percent oxygen, (3) collection of a sample of the exhaled mixture, (4) analysis of the exhaled air, (5) analysis of the initial and exhaled mixture, and (6) mathematical processing of the results.

The composition of the exhaled air was investigated in a Haldane apparatus. The results were used to calculate the arteriovenous oxygen difference (AOD) which, according to Lindgard, is expressed for acetylene by the formula:

$$AOD = \frac{h}{g} i\ (0 - 48.1) \cdot 0.00971,$$

where h is 1 percent oxygen difference between the first and second samples of the mixture, g the same acetylene difference, and B the barometric pressure.

$$i = \frac{C + C^1}{2}$$

where C and C^1 are the concentrations of acetylene in the first and second samples of the mixture.

During the experiments changes were measured in arterial pressure, pulse and respiratory rates, and EKGs were recorded. The dogs were injected intravenously with 1-1.5 mg/kg[1] of chloracizin. The minute volume was determined before administration of the drug, 5 and 40 min later. The results are summarized in table 13.

It is evident from the table that the cardiac output under the influence of chloracizin increased only slightly, averaging 15 ± 6 percent above the original level in 5 experiments. Judging by the significance of the mean difference, the increase in output was not statistically significant ($p > 0.05$ with $t = 2.25$).

Knowing the values of the cardiac output and arterial pressure, we were able to calculate cardiac activity from the formula:

$$W = 13.6 \cdot Q \cdot R + \frac{pv^2}{2g},$$

where Q is the output, R arterial pressure, p weight of ejected blood, v rate at which blood is ejected, g acceleration of gravity, and $\frac{pv^2}{2g}$ expression of the

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[1]Since the experiments were performed under chronic conditions without anesthesia, the doses of chloracizin used were smaller than in the acute experiments.

TABLE 13. EFFECT OF CHLORACIZIN ON CARDIAC OUTPUT AND ACTIVITY[1]

No. of experiment	Time of determination	Arterial pressure in mm Hg	Pulse rate (no. of beats per min)	Respiratory rate (amt per min)	Gas exchange			Arteriovenous difference, in ml/liter	Cardiac output in liters	Cardiac activity in kgm/min
					Pulmonary ventilation	% O_2	Oxygen consumption, in ml/min			
1	Before administration	130	108	24	5.4	4.0	216.0	35.5	6.0	14.5
	After administration	132	120	24	5.4	3.8	205.2	32.6	6.3	16.0
2	Before administration	130	104	22	5.4	3.5	189.0	26.0	7.0	14.0
	After administration	125	120	26	5.8	3.0	178.2	22.0	8.0	18.0
3	Before administration	150	86	20	6.3	2.5	155.0	17.0	8.0	20.0
	After administration	152	100	22	7.6	2.4	182.0	20.0	9.0	24.7
4	Before administration	140	88	20	6.3	3.3	207.9	40.8	5.0	11.8
	After administration	130	120	22	6.7	2.5	167.5	29.5	5.7	12.8
5	Before administration	140	100	20	6.3	3.3	207.9	33.7	6.2	12.2
	After administration	130	120	22	7.2	3.2	230.4	34.0	8.0	17.6

[1]Chloracizin was injected intravenously in a dose of 1 mg/kg. The determinations were made 5 min after injection.

kinetic energy developed by the heart. (Since this energy was insignificant, it was ignored in the calculations.)

Inasmuch as chloracizin does not cause significant changes in arterial pressure, cardiac activity changes in proportion to the change in output. The figures in table 13 show that these changes were slight, averaging 4.4 ± 1 percent with confidence limits of 1.62-7.18.

Thus, chloracizin improves the blood supply conditions of the heart, for it greatly increases the volume rate of the coronary flow without seriously affecting cardiac activity. Moreover, unlike most vasodilators, chloracizin during the first phase of its action (12-15 min after administration) accelerates the volume rate of the coronary flow without at the same time increasing the amount of oxygen consumed by the heart.

It is fair to conclude from an analysis of the effect of chloracizin on the coronary circulation that its ability to dilate the coronary vessels plays an important role in increasing the myocardial blood supply.

We thought it would be interesting to determine the mechanism responsible for its action on the cardiac vessels. We first had to find out whether it is due to the myotropic effect or to its influence on nervous regulation of coronary vascular tone. That chloracizin has myotropic action is beyond question for two reasons. First, in experiments on isolated segments of the intestine, it was found to relax the smooth muscles. Secondly, experiments with perfusion of the isolated cat heart showed that it increased drainage from the coronary vessels 40-45 percent above the original level. Thus, we had to determine whether the effect of chloracizin on nervous regulation of blood flow in the coronary vessels is of any significance in manifesting its vasodilator effect.

Since the vasomotor tone of the coronary vessels is due to the sympathetic nervous system (the vagus nerves apparently are not directly involved in regulating the tone of the cardiac vessels), we began by studying the mechanism of action of chloracizin on the cardiac vessels with experiments in which the drug was administered in a 5 mg/kg dose after denervation of the heart (i.e., after removing the stellate and four thoracic sympathetic ganglia and dividing the cervical sympathetic nerves).

The results of this series of experiments were compared with those obtained after administering the same dose of chloracizin to normal animals. We found that the effect of the drug after denervation of the heart was much weaker, only one-third as powerful as under normal conditions. If we accepted the prevalent view that the vasomotor tone of the coronary vessels is low and assumed that the action of chloracizin is the result of its hampering or blocking the transmission of excitation to the cardiac vessels, we would then have to account for this great difference in the effects of chloracizin in normal and denervated animals. We can only conjecture that the lessened effect of the drug may be due to some extent to the changes in cardiac activity and myocardial metabolism produced by denervation.

Thus, our experiments indicate that the effect of chloracizin on the cardiac vessels is due to its spasmolytic (myotropic) action combined with its ability to hamper the transmission of excitation from the sympathetic nerves to the cardiac vessels. Our next task was to determine just which link in the chain of transmission is involved. Since it is difficult when stimulating the cardiac sympathetic nerves to differentiate changes in the blood supply caused by the reaction of the vessels themselves from the changes produced by extravascular factors, we used as a model in control experiments changes in resistance of vessels in the extremities in response to stimulation of the divided abdominal sympathetic chain. Rectangular impulses at a frequency of 5 cps (duration 5 msec, amplitude 5-10 v) were used for purposes of stimulation. Resistance was recorded by means of a perfusion pump. Stimulation of the abdominal sympathetic chain sharply increased resistance in the vessels of the extremities. Chloracizin in a dose of 2-2.5 mg/kg decreased the intensity of the reaction 70-75 percent and in a 5 mg/kg dose eliminated it entirely. Thus, the results of these experiments showed that chloracizin can hamper the transmission of excitation from the sympathetic nerves to the blood vessels.

To determine whether this effect is related to the drug's influence on the transmission of excitation in the ganglia or in the peripheral adrenergic structures, we studied its influence on the transmission of excitation from the postganglionic fibers to the vessels in the extremities. We recorded the resistance of the vessels supplying the cat gastrocnemius. The animal was anesthetized with ditiline (succinylcholine chloride). Stimulation of the sciatic nerve with rectangular impulses at a frequency of 10 cps (duration 4 msec, amplitude 20 v) sharply increased the resistance of the perfused vessels. A 5 mg/kg dose elicited a much weaker reaction (80 percent of the original value). These experiments showed that chloracizin has sympatholytic properties. However, further experiments revealed that sympatholytic and adrenolytic effects cannot, in general, be combined. The blood pressure and regional resistance reactions to epinephrine and norepinephrine are not only not blocked by chloracizin, but they are actually intensified. Hence, it is fair to assume that the sympatholytic effect of chloracizin is similar in mechanism of action to that of the sympatholytic agents capable of blocking the transmission of impulses from the endings of the adrenergic fibers to the effectors, causing the secretion of epinephrine and norepinephrine to diminish or cease. According to a number of authors, certain choline esters (Hey and Willey, 1954; Willey, 1957; Exley, 1957; Bain and Fielden, 1956) and quaternary benzylammonium salts (Boura and Green, 1959; Boura, Green, McCourbey, et al., 1959) also have this action. It will be noted, however, that these substances (particularly bretilium) have a marked hypotensive effect, whereas chloracizin does not change systemic arterial pressure. The reason for the lack of hypotensive effect is presumably that chloracizin does not influence the transmission of excitation from the sympathetic nerves to various effectors with the same intensity. For example, in therapeutic doses (2-5 mg/kg) it does not change the tone of the third eyelid in cats subjected to electric stimulation of the cervical sympathetic nerve. It affects this object only when administered in massive, virtually toxic doses (15-20 mg/kg).

The experiments described indicate that chloracizin dilates the coronary vessels through its spasmolytic (myotropic) action and by hampering the

transmission of excitation to the cardiac vessels from the endings of the sympathetic nerves responsible for their tonic innervation. The cholinolytic properties of the drug likewise play a definite part in its beneficial effect on the cardiac blood supply. We based this conclusion on 5 experiments in which chloracizin was administered to animals after they were intravenously injected with atropine (1 mg/kg). Under these conditions, when the cholinolytic properties of chloracizin were not manifested, it had a less pronounced effect on the volume rate of the coronary flow, which increased 56 ± 10.2 percent (after atropinization) and 90 ± 9.2 percent under normal conditions. Chloracizin's mechanism of cholinolytic action on the cardiac blood supply thus seems to be similar to the effect of atropine.

Our observations on chloracizin's mechanism of action on the cardiac blood supply are insufficient to warrant drawing definite conclusions regarding all the manifestations of the drug's pharmacological action by which it realizes this effect. We can only say that its antispasmodic, cholinolytic, and sympatholytic properties play an important role.

Our observation that chloracizin is capable of improving the myocardial blood supply suggested to us the possibility of using the drug to treat coronary circulatory disorders. But first we had to determine whether it is superior in this respect to the agents already known. We thought it necessary to compare its effectiveness with that of the drugs currently prescribed for angina pectoris, e.g., papaverine, tiphen (2-diethylaminoethyl diphenylthioacetate hydrochloride), and nitroglycerin. We used as a criterion of effectiveness their capacity to increase the volume rate of the coronary flow. The diagram in figure 30 illustrates the activity of 6 preparations--3 phenothiazine derivatives (chloracizin, mepazine, and chlorpromazine), papaverine, tiphen, and nitroglycerin. The dosage was calculated to produce a maximum increase in the coronary flow without toxic effects. The height of the columns corresponds to the mean values of the coronary flow in percentages of the original level. The confidence limits are indicated for each series of experiments.

It is evident from the figure that the agents can be arranged in the following order according to their capacity to increase the volume rate of the coronary flow: chloracizin, papaverine, mepazine, tiphen, chlorpromazine, and nitroglycerin.[1] The data showing that chloracizin is one of the most effective agents in increasing the cardiac blood circulation led us to make a more detailed study of its pharmacological properties as a prelude to a possible recommendation for clinical use. In investigations conducted jointly with Yu. I. Vikhlyayev (Yu. I. Vikhlyayev and N. V. Kaverina, 1959), we found that the drug possesses marked spasmolytic and cholinolytic action, has low toxicity, and is readily tolerated by experimental animals even after prolonged administration. An important practical feature of the drug is its capacity to correct cardiac arrhythmia (Yu. I. Vikhlyayev and N. V. Kaverina, 1958).

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[1]Note in the diagram the inconsistency between the capacity of nitroglycerin to increase the volume rate of the coronary flow and its clinical effectiveness. This matter was separately investigated and is discussed in detail below.

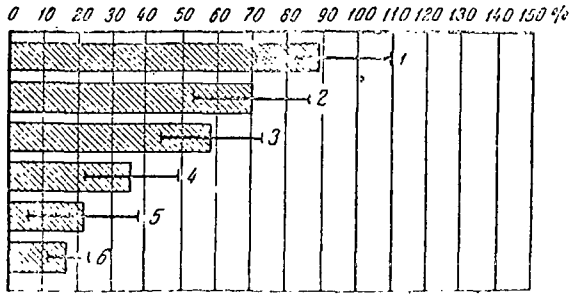

Figure 30. Diagram illustrating the comparative activity of vasodilator agents with respect to their influence on the volume rate of the coronary flow (the mean percentage of increase in coronary flow is shown in the series of experiments with the confidence limits).
1--chloracizin; 2--papaverine; 3--mepazine; 4--tiphen; 5--chlorpromazine; 6--nitroglycerin.

We recommended chloracizin for clinical trials because it combines spasmolytic and anti-arrhythmic action with the capacity to increase the cardiac blood supply. Some idea of its therapeutic value may be gained from the following clinical findings. It was generally used in the treatment of patients with severe forms of coronary insufficiency complicated by atherosclerosis. In some clinics it was given to patients whose angina pectoris was neurogenic, functional in character. The patients given the drug were mostly persons who had previously been unsuccessfully treated with agents ordinarily used for angina pectoris (papaverine, nitroglycerin, validol, etc.).

The drug was used in capsule form because of its mild local irritating and anesthetizing action and to rule out a psychotherapeutic effect. Depending on the form of the disease and on the patient's impression of his condition during the therapy period, chloracizin was prescribed in doses of 15-30 mg to be taken 2-4 times daily. Most of the clinics observed the patients' general condition, intensity of pain, and frequency of anginal attacks. The objective indices included changes in the EKG, arterial pressure, and pulse. For example, patients in the therapy division of the Pavlov Institute of Physiology, USSR Academy of Sciences, received 0.075 g of diuretin, 0.03 g of papaverine, and 0.025 g of luminal (3 times daily for 4-10 days). The pulse rate and intensity of anginal attacks were carefully considered. If the treatment seemed ineffectual and pain continued with the same frequency and severity, chloracizin was prescribed in 15-30 mg doses to be taken 3 times a day (N. A. Rekhtzamer, 1960). In the Institute of Therapy, USSR Academy of Medicine, Ye. V. Erina (1961) used ballistocardiography in addition to the ordinary methods of observation. In the Faculty Therapy Clinic of the Leningrad Institute of Pediatrics, R. S. Ivanov (1960) provided the patients with individual charts on which they were to note their subjective sensations, frequency and severity of anginal attacks, and the effects of nitroglycerin taken before and during chloracizin therapy.

The results of treating patients in 6 clinics were as follows. Chloracizin was given to 287 persons with different forms of coronary insufficiency.

It had a beneficial effect in 194 as shown by decreased frequency or disappearance of anginal attacks, diminution of pain, and general improvement. The results were particularly good in the patients with angina pectoris associated with coronary atherosclerosis. According to Erina (1961), the drug was as effective in patients with the early ischemic stage of coronary atherosclerosis as in those with chronic coronary insufficiency that resulted in cardiosclerosis. This was also the conclusion of S. S. Milovidova (1960). The drug was less effective in treatment of patients suffering from atherosclerosis combined with hypertension or from diseases that may lead to the neurogenic form of angina pectoris. It will be noted that the positive therapeutic effect of chloracizin was accompanied in only a few cases with an improvement in the EKG indices. According to the ballistocardiographic data, chloracizin improved myocardial contractility in patients with the ischemic stage of coronary atherosclerosis. The drug had no effect on arterial pressure or on the pulse rate. Chloracizin was also found to eliminate extrasystoles. In some patients with atherosclerosis of vessels in the lower extremities, it relieved the symptoms of intermittent claudication.

The great majority of patients readily tolerated the treatment, although there were some side effects in a few cases: dryness of the mouth, abdominal distention, nausea, headache, vertigo, unsteady gait, paresthesia, noise in the ears, and marked weakness. These symptoms usually appeared 20-30 min after administration of the drug but they did not last more than 2-3 hours. The patients with hypertension and clinical symptoms of sclerosis of the cerebral vessels were most prone to suffer from these side effects.

It is evident from the foregoing that chloracizin is an effective agent in the treatment of angina pectoris. A particularly valuable feature is that it is active against the chronic forms of coronary insufficiency, i.e., in cases where most of the available agents are ineffectual.

Considerable experience has been gathered in recent years on the clinical use of chloracizin. In 1960 the Pharmacological Committee of the USSR Ministry of Health authorized the release of the drug for broad medical use.

PART II

EFFECT OF PHARMACOLOGICAL AGENTS ON THE CARDIAC BLOOD SUPPLY

CHAPTER 1. SIGNIFICANCE OF REFLEXES IN THE DEVELOPMENT OF ACUTE CORONARY INSUFFICIENCY (CLINICAL AND PHYSIOLOGICAL DATA)

A great many experimental and clinical studies have dealt with the pathogenesis and treatment of angina pectoris. It is now considered an established fact that the basis of angina pectoris attacks is acute coronary insufficiency, which gives rise to myocardial ischemia. Angina pectoris is an acute lack of oxygen in certain portions of the heart muscle accompanied by pain in the cardiac region. "Only a combination of acute myocardial ischemia and the characteristic pain signifies angina pectoris," (G. F. Lang, 1935). However, this definition is applicable only to the final stage of a complex process based on the interaction of various mechanisms which, in combination, determine the clinical course of the different forms of angina pectoris. According to M. S. Vovsi's classification (1958), angina pectoris arising after acute coronary insufficiency is due to neurovascular disorders caused by organic (atherosclerosis or inflammatory lesions of the coronary arteries) or angioneurotic dysfunction of the arterial system responsible for the cardiac blood supply. It is generally held that acute coronary insufficiency is caused by dysfunction of the coronary arteries, which results in a disparity between the oxygen requirements and blood supply of the myocardium.

There have been a great many investigations in recent years on the significance of impaired myocardial tissue metabolism in the origin of coronary insufficiency. This interesting research trend led to the discovery of several facts on changes in biochemical processes in the myocardium that throw light on the pathogensis of coronary insufficiency (M. Ye. Rayskina, 1956, 1957, 1958; Bing, 1959; Raab, 1953, 1959; others). A discussion of these matters is beyond the scope of our monograph. We wish only to mention that, according to Raab (1953), angina attacks result from the accumulation of catecholamines in the myocardium, which sharply increase its oxygen consumption and lead to hypoxia. Hypoxia becomes very severe in coronary sclerosis, a condition that reduces the capacity of the coronary vessels to dilate.

The experimental observations cited by Raab are of independent interest in appraising the role of the sympathetic nervous system in myocardial metabolic changes. The participation of reflexes in the development of angina pectoris cannot be ruled out especially since the pain associated with myocardial hypoxia is independent of the underlying mechanism. It arises from stimulation of the afferent systems which originate the pain impulses. We do not understand why

Raab, in an article dealing with adrenergic and cholinergic influences on myocardial metabolism (1959), writes: "The conception of coronary spasm was a temporary hypothesis at a time when the effect of hypoxia on myocardial metabolism caused by the catecholamines was still unknown."

The existing mass of experimental and clinical material indicates that acute impairment of the coronary circulation and consequent pain is related to the vasomotor tone of the coronary vessels, in which changes are caused mainly by reflex influences spreading to these vessels. The source of afferent impulses seems to be either the heart itself or other internal organs, especially when functionally altered by a pathological process. Accordingly, the investigations designed to elucidate the mechanisms of these reactions can be divided into two groups. One includes the studies on the reflexes arising after experimental impairment of the coronary circulation. Research in this direction started in the 1930s when the idea of myocardial ischemia as an essential precondition for the development of any form of angina pectoris was clearly formulated for the first time (Keefer and Resnik, 1928; Lewis, 1932; G. F. Lang, 1935; others).

Experimental proof of this view was provided by several authors who observed that coronary occlusion in nonanesthetized dogs produced pain accompanied by a set of reactions indicative of an excited autonomic nervous system (Sutton and King, 1928; Pearcy, Pries and Van Allen, 1929; Sutton and Lueth, 1930; Blumgart, Hoff, Landowne and Schlesinger, 1937). These investigators also found that application of a ligature was immediately followed not only by pain but by EKG changes suggestive of impaired myocardial nutrition. Pain diminished only when light anesthesia (morphine) was used (Singer, 1926).

The conclusion drawn from these experiments was that ischemia arising from occlusion of a coronary vessel stimulates the sensory nerve endings, causing both pain and further deterioration of the myocardial blood supply. However, some investigators maintain that myocardial ischemia is not the only mechanism responsible for pain in angina pectoris. For example, Katz and coauthors (Katz, 1935; Katz, Mayne and Weinstein, 1938; Robertson and Katz, 1938) found that the nerve endings of the afferent fibers, stimulation of which produces cardiac pain, are embedded not only in the walls of the coronary vessels, but in the nerve plexuses that surround them. These authors discovered that occlusion of a portion of the coronary artery of nonanesthetized dogs carefully separated from the surrounding tissues did not produce sharp pain, whereas compression of a vessel with its surrounding tissue intact did.

Other investigators demonstrated that sudden total occlusion of a coronary vessel may cause reflex constriction of other cardiac arteries. Manning et al. (Manning, McEachern and Hall, 1939, 1940) observed that occlusion of the anterior descending branch of the left coronary artery killed 40 percent of the nonanesthetized dogs as compared with only 10 percent of the anesthetized animals. They believe that the direct cause of the animals' death was a reflex spasm of the collateral and smaller arteries that widened the field of myocardial ischemia.

These findings were confirmed by other investigators (Le Roy and Snider, 1941; Le Roy, Fenn and Gilbert, 1942; Blumgart, 1947) who discovered that ligating the reflex branch of the left coronary artery immediately constricts the other cardiac arteries. Le Roy et al. recorded this phenomenon on color film. They compared their data with clinical observations where in many cases of myocardial infarct that immediately caused death, histological examination failed to reveal any marked changes in the myocardial blood supply. The authors believe that the reason for the sudden death of patients with a myocardial infarct may be a reflex that constricts the coronary vessels. The afferent pathway of this reflex proceeds from the site of the infarct.

N. V. Il'ichevich and V. A. Kozak (1959) recorded EKG changes in dogs with an occluded coronary vessel. They found that a sudden total occlusion of the artery immediately induced sharp changes in the EKG, whereas gradual occlusion induced indistinct changes. They concluded that the EKG changes associated with acute impairment of the myocardial blood supply are reflex in nature. V. V. Frol'kis (1959) reached a similar conclusion after experiments in which changes in cardiac activity caused by ligating one of the coronary vessels were weakened by section of extracardiac nerves.

The presence of reflex vasoconstrictor influences on the coronary vessels after ligation of other cardiac arteries was subsequently confirmed by experiments that were procedurally more rigorous. A. V. Lebedinskiy et al. recorded the volume rate of the blood flow in one of the cardiac arteries by the thermoelectric method. They found that ligation of one of the coronary vessels caused a reflex decrease in the coronary blood flow of other cardiac arteries (A. V. Lebedinskiy, V. I. Medvedev and I. A. Peymer, 1953; A. D. Golendberg, 1954; A. V. Lebedinskiy and V. I. Medvedev, 1947). It will be noted, however, that such a decrease was not observed in all the experiments involving the ligation or occlusion of a cardiac artery. For example, Opdyke and Selkurt (1948) in an acute experiment involving the ligation of a cardiac artery and recording of the blood flow in other branches of the coronary arteries observed a decrease in only 2 out of 10 cases.

Wang et al. (Wang, Frank, Kanter and Wegria, 1957) occluded a coronary artery for 1-2 min, but failed to observe any reflex decrease in blood flow in the descending and reflex branches of the left coronary artery. They believe, however, that their experiments do not warrant ruling out the possibility of reflex constriction of arteries because the innervation of the latter may be impaired by the cannulas introduced to measure the blood flow.

Some experimental and clinical observations indicate that myocardial infarcts are frequently complicated by acute insufficiency of the blood supply of other nonthrombosed vessels. Most authors are inclined to ascribe these phenomena to a reflex spasm of the coronary vessels resulting from stimulation of the nerve endings in the region of the infarct. It is interesting to note that in these cases the infarct was immediately followed by EKG changes (T wave and position of the S-T segment) at the leads characterizing the state of those portions of the myocardium lying beyond the region of the infarct (Gilson and Day, 1953; Scherf and Boyd, 1955; D. Mendl and N. Kenedi, 1958).

The conclusion to be drawn from the literature cited above is that impairment of the cardiac blood supply by pathogenetic factors can often be intensified by reflexes that facilitate the development of acute coronary insufficiency.

Reflexes originating in different parts of the body and resulting in change in the coronary vascular tone are another factor that contributes to deterioration of the cardiac blood supply.

There are many instances in which experimental data have been the basis for correct evaluation of clinical observations. But in the case of visceral reflexes and their influence on angina pectoris, the clinical observations were far ahead of the experimental data. A century ago S. P. Botkin, after observing patients with angina pain diagnosed as having a floating kidney or inflammation of the biliary tract, conjectured that these phenomena might be reflex in origin (S. P. Botkin, 1867). In 1881 his coworker N. P. Simanovskiy found that stimulation of the sensory nerves may affect cardiac activity.

The existence of a reflex mechanism underlying the genesis of angina pectoris has been confirmed by a mass of experimental and clinical material (K. K. Monakhov, 1927; B. A. Yegorov, 1929; L. F. Dmitrenko, 1930, 1938; E. Mandel'shtam, 1931; D. G. Popov, 1936; N. P. Afonskiy, 1936; G. F. Lang, 1936; M. S. Vovsk. 1957, 1958; I. A. Levin, 1956; N. A. Al'bov, 1942, 1958; others.

The so-called angioneurotic forms of angina pectoris are well known. These forms include the angina pectoris whose genesis is promoted by reflexes from pathologically changed viscera (M. S. Vovsi, 1958). The literature on the subject is extensive (G. F. Lang, 1935; Radvanyi and Gellert, 1936; V. A. Triger and R. O. Yasinovskaya, 1938; V. F. Zelenin, 1939; Morrison and Swalm, 1940; G. A. Brandenburgskiy and Ye. L. Tovbina, 1949; G. A. Brandenburgskiy and I. Ya. Balaban, 1949; Freedberg and Risman, 1953; I. A. Chernogorov, 1954; Schmidt and Biork, 1955; V. A. El'berg and M. B. Feygin, 1958; A. F. Epshteyn, 1959).

We shall not go into detail on the cases of angina pectoris caused by reflexes from a pathological focus in any of the viscera and merely note that, according to the literature, pathological processes in the stomach, gallbladder, and other abdominal organs are the commonest sources for symptoms of this kind. It is also worth mentioning that the reflex component of angina pectoris is most clearly manifested in cases where the myocardium or the cardiac vessels have been pathologically changed. "We should like to emphasize that neuroreflex influences play a major role in the genesis of the above-mentioned forms of angina pectoris against a background of coronary sclerosis and angiitis" (M. S. Vovsi, 1958). These clinical observations were confirmed by numerous experimental investigations. For example, Laplan and Pautrats (1950) observed myocardial infarcts originating in dogs injected with croton oil (into aortic adventitia) during a sterile operation. The authors believe that impairment of the coronary circulation that led to the infarction was caused by a reflex from the aortic receptors.

I. Ye. Ganelina (1955) performed experiments on rabbits with experimentally induced neurogenic hypertension and atherosclerosis. She found that stimulation of the intestinal or urinary bladder mechanoreceptors caused sharp

EKG changes indicative of impairment of the myocardial conduction system or nutrition. The latter type of changes were very pronounced after stimulation of the intestinal receptors. Ganelina (1958) showed that EKG changes are most marked in animals with atherosclerosis following stimulation of the gastrointestinal chemoreceptors. These data are consistent with the clinical observations on patients with atherosclerosis in whom stimulation of the gastric chemoreceptors with table mustard impaired atrioventricular conduction and lowered the T_1 and T_2 waves.

Thus, visceral reflex influences on the heart are most pronounced in atherosclerosis. Reflexes to the heart were also found by other experimental techniques used to induce pathological changes in the myocardium. For example, V. N. Chernigovskiy (1952) cites data obtained in his laboratory by Ye. Ye. Epshteyn whereby stimulation of the duodenal mechanoreceptors in rabbits injected intravenously with barium chloride caused paroxysmal tachycardia and a negative T wave to appear on the EKG.

B. I. Trusevich (1958) used a similar method. According to this author, an extrasystole and paroxysmal tachycardia may appear after inflation of the duodenum and gallbladder only in animals in which intravenous injection of barium chloride has caused pathological changes in the myocardium. It is worth noting that the EKG changes indicative of an insufficient cardiac blood supply were most pronounced after stimulation of the gallbladder. These changes were alleviated by nitroglycerin or by excluding the receptors by means of anesthesia.

According to Ye. Ye. Epshteyn (1956), the presence of pathological changes in the myocardium is not essential for inducing changes in the EKG by stimulating the gallbladder receptors. Similar observations are cited by Yu. A. Petrovskiy and L. B. Maksimovich (1954).

Angina pectoris is recognized as a disease whose course is determined by the state of the higher divisions of the central nervous system. Those interested in the subject are referred to the works of N. D. Strazhesko (1925, 1955), G. F. Lang (1935), M. M. Gubergrits (1950), B. V. Il'inskiy (1954), and others. The clinical observations have also been confirmed experimentally.

The basis for studying these complex matters was I. P. Pavlov's method of conditioned reflexes. Impairment of CNS function by the method of conflicting conditioned reflexes (e.g., food and defense) or a combination of conditioned and unconditioned stimuli changes cardiac activity (V. P. Lekishvili, 1954; M. B. Feygin, 1954; Ye. G. Petrova, 1954; V. V. Frol'kis, 1959). The phenomenon can be readily seen in monkeys. For example, G. O. Magakyan, D. I. Miminoshvili and G. Ya. Kokaya (1956) observed coronary insufficiency and myocardial infarcts in monkeys following a disruption of higher nervous activity. Their findings were confirmed by other authors.

According to G. M. Cherkovich (1959), neurosis in monkeys induced by disruption of the daily rhythm resulted in acute coronary insufficiency. Microneroses were found in the myocardium of the dead animals. Interesting data are reported by S. I. Teplov (1958) who after forming a conditioned reflex to the injection of pituitrin in dogs was able to impair the animals' coronary circulation.

The observations of L. A. Koreysha (1958) provide genuine confirmation of the enormous role played by the state of the CNS in the pathogenesis of impaired coronary circulation. According to his data, superintense stimulation of the brain during neurosurgery on human patients may cause acute disorders of the coronary circulation that frequently result in death.

It is obvious, therefore, that the functional state of the higher divisions of the brain as well as reflex influences from various viscera or from the receptors of the coronary vessels themselves play an important part in impairing the cardiac blood supply. It should be noted, however, that this conclusion is based mainly on experimental and clinical observations in which EKG changes served as indices of the state of the myocardium. Although highly valuable in the clinic, this method is not accurate enough to evaluate the mechanisms underlying impairment of the coronary circulation.

These problems naturally cannot be solved without more adequate methods of recording the state of the myocardial blood supply after the use of agents that impair it. This view motivated several investigations in which change in the volume rate of the coronary flow was studied after the presentation of a variety of afferent stimuli.

Reflexes from the carotid sinus receptors to the coronary blood flow were studied in detail in 1931 by Hochrein and Keller, who found that occlusion of both carotid arteries induced dissimilar changes in the coronary flow. The rate generally increased after stimulation of the carotid sinus receptors, but in some cases it decreased. Stella (1931) observed in experiments in a heart-lung-brain preparation of dogs that raising the pressure in the region of the carotid sinus under perfusion conditions reduced the volume rate of the coronary flow.

Jourdan and Faucon (1959) obtained analogous results in experiments on intact animals. However, their experiments cannot be considered convincing because to obtain stable cardiac blood supply conditions they used a sympathectomy, obviously relying on the view of some authors that vagus influences are predominant in maintaining coronary vascular tone. It is no surprise, therefore, that Marcou and Carbunesco (1934) obtained directly opposite results in animals with intact innervation. In their experiments an elevation of pressure in the carotid sinus region increased the coronary flow rate.

Heidenreich and Schmidt (1956) recorded the rate of the coronary flow in dogs after stimulating the afferent fibers of the vagus nerves and carotid sinus receptors. They found that the coronary flow generally increased after such reflex influences. Greene too (1935) studied reflex changes in the coronary flow after stimulating afferent nerves. He showed that stimulation of the afferent fibers of the sciatic, splanchnic, phrenic, and vagus nerves induces reflex changes in the coronary flow. The response of the coronary flow to stimulation of the afferent nerves was irregular. In most cases it increased, but in a few cases it decreased.

Finally, in some experiments the reflex response was two-phase: brief decrease in the blood flow followed by an increase. A. V. Tonkikh, A. I. Il'in,

and S. I. Teplov (1959) observed a phase reaction of the coronary flow in response to painful stimulation of the afferent fibers of the sciatic nerve. In their experiments an initial decrease in the coronary flow was followed by an increase.

Reflex changes in the coronary flow following stimulation of the visceral receptors are equally inconsistent. This is no doubt due to the ambiguous results obtained by different investigators of the problem. Hinrichsen and Ivy (1933) found that stimulation of the afferent nerves in the abdominal cavity generally intensified the coronary flow. Gilbert, Le Roy and Fenn (1940), who investigated changes in the blood flow of cardiac vessels in dogs after inflation of the stomach and gallbladder, came to the conclusion that a decrease in the blood flow is the commonest reaction.

G. N. Aronova (1953, 1956) also studied interoceptive reflex influences on the coronary circulation. According to her data, stimulation of the mechanoreceptors of the urinary bladder or small intestine did not regularly change the coronary flow. It generally increased, but in some cases it decreased. The latter reaction is more characteristic of animals with experimental myocardial infarct.

In summing up the experimental and clinical data presented in this chapter, we may say that reflexes arising both from the cardiac region proper due to impairment of myocardial metabolism and from the viscera, especially when in a pathological state, play a major role in the origin of angina pectoris. These reflexes may spread to the cardiac vessels and impair their function, thereby causing the myocardial blood supply to deteriorate.

It is clear from the foregoing that elimination of reflexes of this kind is one of the ways of exerting a pharmacological influence on the cardiac blood supply.

CHAPTER 2. METHODS OF STUDYING REFLEXES TO THE CORONARY VESSELS AND THEIR PHYSIOLOGICAL CHARACTERISTICS

Although the reflexes of coronary vessels have been repeatedly investigated, the ways in which the reflexes are executed are still unclear. This is not surprising in view of the technical difficulties involved in studying nervous regulation of the cardiac vessels. The usual method of evaluating the cardiac blood supply by recording the volume rate of the coronary flow does not permit the differentiation of changes in vascular tone from the hemodynamic and extravascular influences.

The response of the coronary flow to afferent stimulation depends on which factors are predominant, for the level of the cardiac blood supply is determined by their interaction. Therefore, when recording the volume rate of the blood flow during stimulation of the afferent pathways, one can observe a variety of responses. This is illustrated by figure 31 which shows three types of reactions following stimulation of the central segment of the tibial nerve. Note that the coronary flow is more often intensified than reduced by stimulation of the afferent pathways. In this respect our observations are consistent with the published data (Hinrichsen and Ivy, 1933; Gilbert, Le Roy and Fenn, 1940; G. N. Aronova, 1953).

It does not follow from the foregoing, however, that a reflex increase in the coronary flow signifies the absence of vasoconstrictor impulses traveling to the coronary vessels. Afferent stimulation generally causes reflex elevation of blood pressure, which facilitates mechanical dilatation of the cardiac vessels and may mask their response to the nerve impulses reaching them.

We have already mentioned that several investigators found that a decrease of the coronary flow after reflex action and EKG changes indicative of impairment of the cardiac blood supply regularly occur when the myocardium is changed by some pathological process (e.g., in atherosclerosis, experimental myocardial infarct, myocarditis, etc.) (Ye. Ye. Epshteyn, 1956; G. N. Aronova, 1956; I. Ye. Ganelina, 1955, 1958; B. I. Trusevich, 1958; others). Hemodynamic regulation of the coronary flow which helps to maintain a certain level of the myocardial blood supply presumably becomes inadequate when the coronary circulation is impaired. Thus, myocardial function, coronary vascular tone, and state of hemodynamic regulation seem to determine in each individual case the nature of coronary blood flow changes in response to afferent stimulation.

It is clear, then, that reflexes of the cardiac vessels cannot be analyzed without a method of determining what they are. In studying the effect of pharmacological agents on reflexes of the cardiac vessels, one must have precise information on the nature, magnitude, and methods of execution of these reflexes.

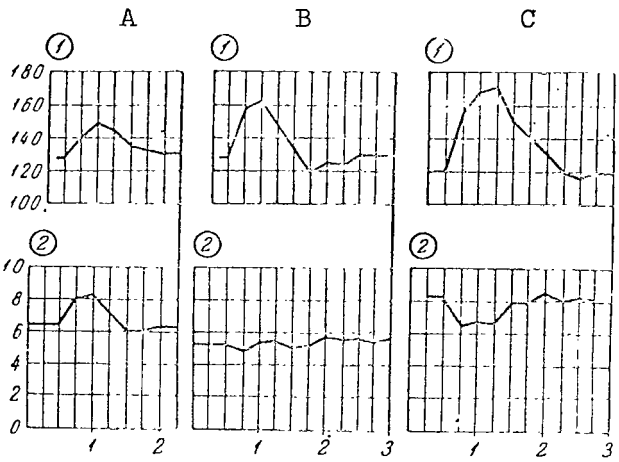

Figure 31. Types of responses of the coronary blood flow to stimulation of the afferent fibers of the tibial nerve. Ordinate: 1--blood pressure changes in mm Hg, 2--changes in volume rate of the coronary flow in ml/min. Abscissa: time in minutes; A--increase in volume rate of the coronary flow after reflex elevation of systemic arterial pressure; B--absence of coronary flow response to reflex elevation of arterial pressure; C--decrease in volume rate of the coronary flow after reflex elevation of systemic arterial pressure.

Since there are no concrete data of this kind in the literature, we performed a series of experiments to develop an adequate technique of determining the reflexes of the cardiac vessels and their physiological characteristics. We found that the method of resistography made it possible to exclude hemodynamic influences on the coronary vessels and was thus convenient for studying their reflexes. We used the technique to observe and quantitatively evaluate changes in resistance of the coronary vessels induced by impulses transmitted to these vessels reflexly. Reflex changes in coronary vascular tone were produced by electric stimulation of the central segments of the tibial and median nerves in the form of rectangular pulses at a frequency of 50-60 cps, 1-2 msec in duration, and with an amplitude of 2-10 v. In some experiments the carotid sinus receptors were stimulated (occlusion of a carotid artery). We found that stimulation of the afferent nerves resulted in reflex increase of resistance in the cardiac vessels. Occlusion of the carotid arteries elicited the same response (fig. 32).

Since an increase in resistance is determined not only by the blood vessels themselves but by extravascular factors, we thought it worthwhile to ascertain the extent to which these factors participate in the observed reactions. We performed experiments to compare the magnitude of changes in perfusion pressure after a reflex to the coronary vessels elicited by stimulating the tibial nerve or by occluding the aorta. Those parameters of nerve stimulation and degree of aortic occlusion were selected whereby pressure in the left ventricle

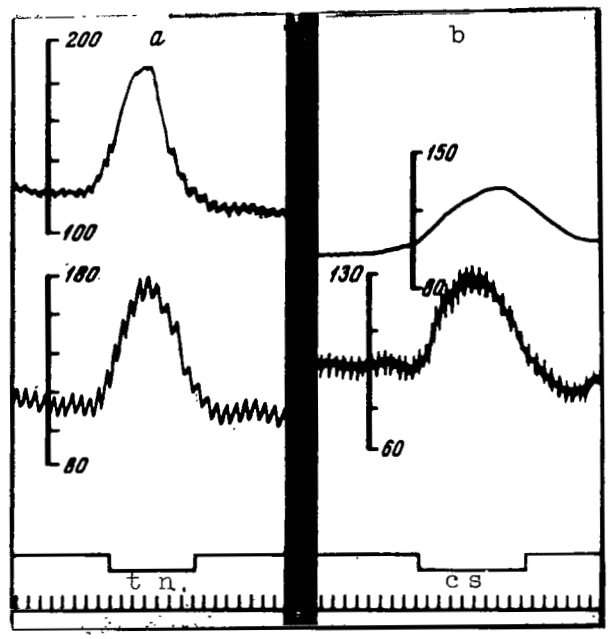

Figure 32. Reflex changes in resistance of the coronary vessels after stimulation of the afferent fibers of the tibial nerve and receptors of the carotid sinus.
Top to bottom: perfusion pressure--resistance of the coronary vessels, blood pressure, stimulation mark, time mark--5 sec. On the left: reflex to the coronary vessels and blood pressure caused by electric stimulation of the afferent fibers of the tibial nerve (stimulation effected by rectangular impulses with these parameters: 7 v, 50 cps, 1 msec). On the right: reflex to the coronary vessels and blood pressure caused by lowering of pressure in the region of the carotid sinus (occlusion of the carotid arteries).

as measured by an electric manometer was equal. We found that with equal values of intraventricular pressure, perfusion pressure (i.e., resistance of the coronary vessels) became 2-1/2 times greater after a reflex than after aortic occlusion. Analysis of the data showed that the difference between these effects was statistically significant ($p < 0.02$) (table 14).

Thus, we found that the main factor responsible for reflex increase in resistance of the coronary vessels is their constriction.

We then performed experiments designed to clarify the route of the reflex arc of the reflexes leading to constriction of the coronary vessels. We pointed out above that in comparing reflexes to the cardiac vessels caused by stimulating various afferent pathways (reflexes from the tibial and median nerves and from carotid sinus receptors), we failed to detect any significant differences between them. We therefore thought that the main objective of this series of experiments should be to elucidate the influence exerted by the vagus and

TABLE 14. CHANGES IN INTRAVENTRICULAR, BLOOD (IN mm Hg), AND PERFUSION (AS PERCENTAGE OF ORIGINAL LEVEL) PRESSURE AFTER REFLEX REACTION AND AORTIC OCCLUSION

	Reflex from tibial nerve					Aortic occlusion			
No. of experiment	intraventricular pressure	blood pressure	perfusion pressure	average % of changes in perfusion pressure	intraventricular pressure	blood pressure	perfusion pressure	average % of changes in perfusion pressure	level of significance
1	30	26	14		30	35	6		
2	70	60	11		70	70	4		$p < 0.02$
3	80	32	8	11 ± 1.2%	80	43	3	4 ± 0.6%	$t = 3.58$
4	30	22	11		30	20	4		$n = 6$

sympathetic nerves on the coronary vessels. The experiments were naturally started by comparing the magnitude of the reflex under normal conditions and after exclusion of impulses traveling to the heart along the vagus nerves. Figure 33a is the kymogram of an experiment in which bilateral vagotomy followed recording of the original magnitude of the reflex. It is evident from the figure that a vagotomy resulted in increased resistance of the coronary vessels and their reflexes.

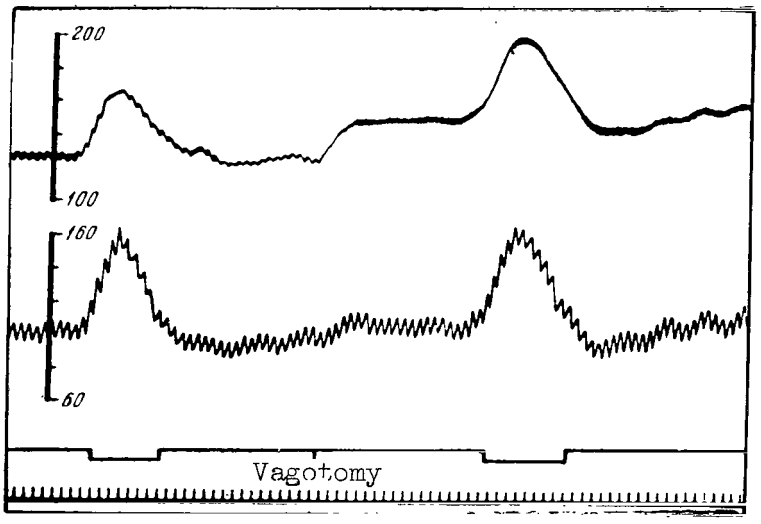

Figure 33a. Reflexes to the coronary vessels and blood pressure caused by stimulation of the tibial nerve before and after bilateral vagotomy. Top to bottom: perfusion pressure (resistogram), blood pressure, stimulation mark, time mark--5 sec.

The injection of atropine (1 mg/kg) had no significant effect on the magnitude of the reflexes to the coronary vessels. The difference between the effects after vagotomy and atropinization is probably due to the fact that the former interrupts the flow of afferent impulses to the vasomotor center from the receptor fields of the major thoracic and cordiac vessels. These impulses, like impulses from the sinocarotid zone, promote tonic inhibition of the vasomotor center, whereas blocking them disinhibits it, thus intensifying the vasoconstrictor effects.

Our observations, therefore, suggest that the vagus nerves do not participate directly in the realization of vasoconstrictor effects on the coronary vessels. We then performed experiments in which we excluded impulses traveling to the cardiac vessels along the sympathetic nerves. We compared the magnitude of these reflexes under normal conditions and after sympathectomy (i.e., extirpation of the stellate and four thoracic sympathetic ganglia and section of the cervical sympathetic nerves). Sympathectomy caused a sharp decrease in the magnitude of reflexes to the cardiac vessels (80-85% below the original level) (fig. 33b). Reflexes to blood pressure likewise decreased somewhat (by 15-20%), apparently due to surgical trauma.

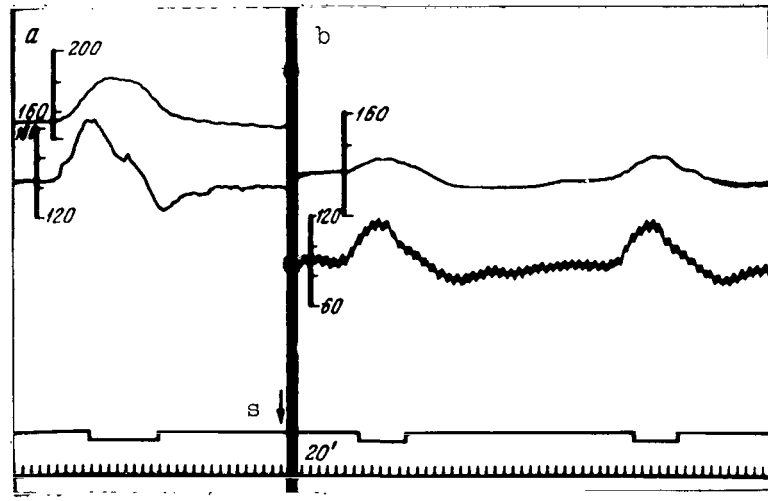

Figure 33b. Decrease in magnitude of reflexes to the coronary vessels after section of sympathetic nerve pathways to the heart. Top to bottom: perfusion pressure, blood pressure, stimulation mark, time mark--5 sec.

a - before sympathectomy; b - 20 minutes later

The slight increase in resistance of the coronary vessels in response to stimulation of the afferent systems that persisted after sympathectomy may have been due to extravascular and hemodynamic influences. Experiments with dihydroergotamine (1 mg/kg), which completely inhibited reflexes to the cardiac vessels, partly confirm this conjecture. By blocking the efferent part of the reflex arc of the generalized vasomotor reflexes, dihydroergotamine

nullifies the hemodynamic effect of reflex elevation of blood pressure on the cardiac vessels.

Our observations indicate that the vagus nerve does not participate directly in the conduction of vasoconstrictor impulses to the coronary vessels. Reflex constriction apparently takes place through the sympathetic pathways.

Our findings contradict the old and well established view that vasoconstrictor impulses to the coronary vessels travel along the vagus nerves (Morawitz and Zann, 1912; Anrep and Segall, 1926; Rein, 1931-1932; Golwitzer-Meier and Krüger, 1935; others). However, as we noted above, convincing experimental data have been obtained in recent years which testify to the absence of direct vagus influence on the coronary vessels (Schreiner, Berglund, Borst, and Monroe, 1957; Denison and Green, 1958; Szentivanyi and Nagy, 1959; Wang, Blumental, and Wang, 1960). The idea that the vagus nerve may possibly have a constricting effect on the coronary vessels apparently rose from the use by various investigators of methods of studying the coronary circulation that did not permit differentiation of changes in vascular tone from hemodynamic and extravascular influences (arterial pressure, cardiac activity, etc.). Actually, if we analyze the experimental conditions in which the results suggestive of vagus vasoconstrictor influence were obtained, we see that these observations were based largely on recordings of the rate of the coronary blood flow, the response of which reflects the interaction of changes in vascular tone with extravascular and hemodynamic influences.

Thus, our views belong with the many observations on increased coronary flow after stimulation of the cardiac sympathetic nerves and administration of epinephrine.

It is also interesting to note that our observations on the role of the sympathetic nerves in the conduction of vasoconstrictor impulses to the coronary vessels agree with the clinical data which indicate that attacks of angina pectoris are accompanied by symptoms suggestive of excitation of the sympathetic nervous system.

CHAPTER 3. EFFECT OF PHARMACOLOGICAL AGENTS ON REFLEXES OF THE CONORARY VESSELS

The investigations of V. V. Zakusov and coworkers (1947, 1953) showed convincingly that the sensitivity to drugs of the central links of the reflex arcs of different reflexes varies within very broad limits. Therefore, the use of pharmacological agents undoubtedly opens up broad opportunities for selective action on certain reflexes. The need to study and search for pharmacological agents capable of altering the reflexes of the coronary vessels is obvious in view of the significance of the reflex factor in the development of angina pectoris.

We thought it would be of most value to investigate neurotropic agents capable of blocking any of the links in the reflex arc of reflexes to the coronary vessels. Since we were particularly interested in the drugs used to treat coronary insufficiency, we started with analgesics.

1. Analgesics

We have already pointed out that, in general, analgesics do not have the capacity to increase the cardiac blood supply. Experiments have shown that among these agents (e.g., morphine, thecodeine, demerol, and methadon), only morphine increases the volume rate of the coronary flow, whereas the others tend to increase the tone of the cardiac vessels. However, it is known from clinical observations that analgesics can halt attacks of angina pectoris.

According to our data, the effectiveness of these substances in angina pectoris is not related to their direct action on the cardiac vessels. Their clinical effectiveness is presumably due only to their relieving the pain syndrome which regularly accompanies angina attacks. But the appearance of pain during such attacks is the first sign that the ailing heart has become a source of afferent impulses, which may also give rise to reflexes that contribute to further deterioration of the myocardial blood supply. It was natural, therefore, to assume that analgesics improve the blood supply by blocking reflexes to the cardiac vessels.

The foregoing considerations led to investigations of the effect of analgesics on coronary reflexes. The results proved to be highly contradictory. Most of the investigations, which date back to the late 19th and early 20th centuries, focused on morphine. In 1877 Witkowski discovered that elevated blood pressure in cats induced by stimulating the afferent fibers of the sciatic nerve is not affected by small doses of morphine, but in large doses it tends to decrease the magnitude of the reflex reaction. This was also the conclusion of Amsler and Beiträger (1923), who found that the injection of large doses of morphine in readily curarized rabbits did not slow the pulse after stimulation of the sciatic nerve. Vercauteren (1932a, b), investigating the effect of morphine on reflex changes in blood pressure

after stimulation of the carotid sinus receptors, concluded that small doses of morphine can inhibit these reflexes. Schmidt and Livingston (1933) also observed a decrease in the magnitude of vasomotor reflexes under the influence of morphine. They further observed that morphine inhibited the reaction of the vasomotor center to asphyxia and administration of carbon dioxide. Similar results were obtained by Raab and Friedeman (1936), who observed a decrease in pressor responses to the administration of carbon dioxide in patients given morphine. They concluded that morphine is capable of inhibiting the vasomotor center.

Information concerning the effect of other analgesics on cardiovascular reflexes is meager. Z. N. Ivanova (1958) found that promedol can inhibit the cardiovascular and respiratory reflexes that arise in response to stimulation of the lower respiratory tract. Inhibition of the reflexes to blood pressure that arise after occlusion of a coronary artery was noted by M. Yu. Ladinskaya (1959).

Thus far we have mentioned only investigations whose authors observed that analgesics inhibit cardiovascular reflexes. However, many investigators obtained completely opposite results. For example, there are references in the literature to morphine increasing reflex bradycardia caused by stimulating the carotid sinus receptors (Jackson and Ewing, 1914; Tomaszewski, 1938). Some investigators observed an increase in the reflexes to blood pressure following stimulation of the carotid sinus receptors and afferent nerves (Kisch, 1921; Albert, 1927; Hering, 1927; Van der Linden, 1932). According to R. P. Kruglikova-L'vova (1953), morphine and promedol increase the reflexes to blood pressure that follow stimulation of the interoceptors of the urinary bladder. G. V. Kovalev (1958), who also studied the effect of analgesics on vascular reactions produced by stimulation of the interoceptors, reached the same conclusion.

It is evident from the literature that the results of research on the analgesics are contradictory. Moreover, there is no published information concerning the effect of analgesics on coronary vasomotor reflexes. Yet study of the influence of analgesics on nervous regulation of blood circulation is not only of considerable interest with respect to their mechanism of action, but of direct practical value. This is particularly applicable to their effect on nervous regulation of coronary vascular tone, which largely determines the severity of angina attacks.

Our experiments showed that analgesics in relatively small doses can inhibit reflexes to the cardiac vessels. This effect was manifested both in experiments involving the recording of reflex changes in the volume rate of the coronary flow and in experiments when the resistographic method was used. Since the results we obtained from the use of both methods were identical, we subsequently restricted ourselves to the resistographic method in studying the effect of pharmacological agents on these reactions because it permits quantitative calculation of the comparative effectiveness of drugs with respect to reflex changes in coronary vascular tone. The experiments performed to study the effect of a 1 mg/kg dose of morphine on reflex changes in coronary resistance were statistically processed. Judging by the criterion of

significance of the mean difference, the inhibiting effect of morphine on these reactions had a high level of significance ($p < 0.002$). In 7 experiments, this dose of morphine inhibited the reflexes to the coronary vessels after stimulation of the tibial nerve by 63±6.2 percent on the average. The reflexes to blood pressure in the same experiments were less inhibited. The decrease in magnitude of these reflexes was 34±10.7 percent. The effect of morphine was transient. Within 15-18 minutes of injection the reflexes returned to the original level (fig. 34). It is interesting to note that when the dose was increased to 2.5-3 mg/kg, the effect on the coronary vessels was not intensified. Moreover, in several experiments the injection of 3-4 mg/kg of morphine intensified the reflexes 10-15 percent above the original level.

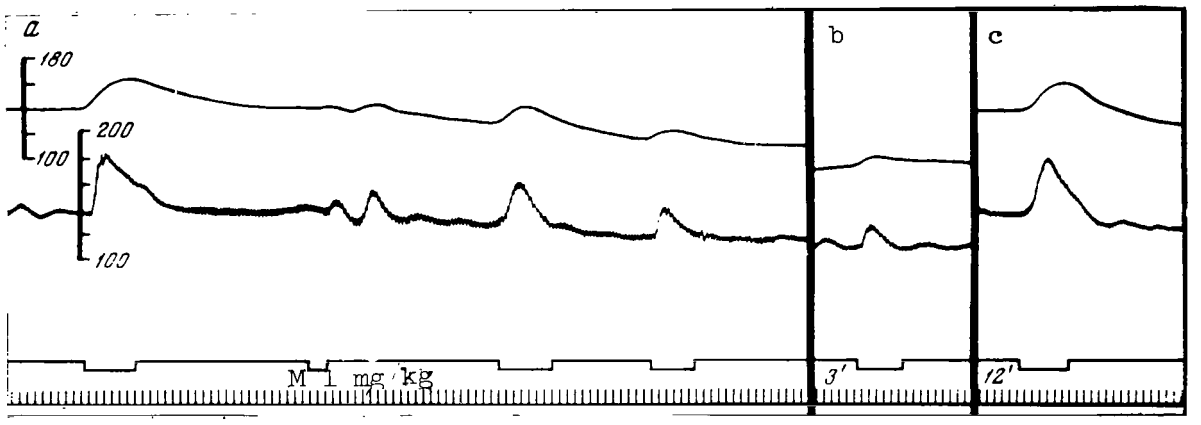

Figure 34. Effect of morphine (1 mg/kg) on reflex changes in resistance of the coronary vessels and blood pressure after stimulation of the afferent fibers of the tibial nerve. Top to bottom: perfusion pressure, blood pressure, mark of stimulation and injection of the agent, time mark--5 sec.

a--background and injection of morphine; b--inhibition of reflexes; c--restoration of reflexes to original level.

The increase in the reflexes lasted a fairly long time (1-1/2 - 2 hours). Owing to the method used, we were unable to observe their return to the original level.

Thecodeine has a similar effect on the coronary vascular reflexes. It will be noted, however, that the action of this drug is more pronounced when administered in smaller doses. For example, in doses of 0.3-0.5 mg/kg it inhibited the reflexes by 30-40 percent of the original values. The significance level of the inhibiting effect of thecodeine on cardiovascular reflexes was $p < 0.001$ when used in a dose of 1 mg/kg.

Statistical processing of the results of experiments in which the effect of this dose of thecodeine on cardiovascular reflexes was investigated after

stimulation of afferent fibers of the tibial nerve revealed that they were inhibited by 76±10.2 percent (mean of 6 experiments). In some cases the drug suppressed the reflexes entirely. It also inhibited blood pressure reflexes. For example, in the above-mentioned series of experiments with stimulation of the tibial nerve, the pressor vascular reflexes were inhibited by 66±2.7 percent. The effect was transient (it lasted no more than 12-15 minutes). When administered in large doses (3-3.5 mg/kg), thecodeine, like morphine, intensified the cardiac reflexes.

Demerol is likewise capable of inhibiting cardiac reflexes. After administration of 0.3-05 mg/kg, the reflexes decreased 75-80 percent of the original values. The significance level of the inhibiting action of promedol on the coronary vascular reflexes was $p < 0.01$ when used in a dose of 1 mg/kg. In 6 experiments this dose inhibited the reflexes 69±6.6 percent on the average. Blood pressure reflexes in the same experiments were inhibited 66±2.7 percent, the effect lasting 16-18 minutes. When the dose was increased to 2-3 mg/kg, the effect was not intensified. Larger doses usually failed to change the magnitude of the reflexes. Sometimes the reflexes increased slightly (5-6 percent above the original magnitudes).

The administration of methadon in doses of 0.3-0.5 mg/kg decreased the reflexes 30-50 percent, but a dose of 1 mg/kg often completely suppressed the reflexes of the cardiac vessels. Statistical processing of the results of the experiments in which the effect of methadon on coronary vascular reflexes was investigated after stimulation of the tibial nerve revealed that they were inhibited 82±8.1 percent. Blood pressure reflexes in the same experiments were inhibited 65±8.6 percent. The effect of methadon was more prolonged than that of the other analgesics. The reflexes became normal 30-35 minutes after the drug was administered.

The administration of large doses of methadon in our experiments was difficult because in doses of 2-3 mg/kg the drug affects cardiac activity and sharply lowers blood pressure.

Our observations showed that all the analgesics under investigation when administered in relatively small doses inhibit the reflexes of the coronary vessels. These doses can be considered more or less equivalent to therapeutic doses. The figures obtained after statistical processing of the results are presented in table 15. This processing included only the experiments in which the reflexes were elicited by stimulating the afferent fibers of somatic nerves, the magnitude of which is unaffected by changes in the level of arterial pressure. The changes in carotid sinus reflexes for which this factor has significance were not taken into account in the statistical processing.

It is evident from table 15 that methadon is more powerful than morphine in inhibiting coronary vascular reflexes. The differences in the effect exerted by the other analgesics are statistically insignificant. Some idea of the comparative activity of these substances may be obtained from figure 35, where the results of experiments with analgesics are represented graphically with the confidence limits. It is also interesting to note that morphine has a somewhat more inhibiting effect on coronary vascular reflexes than on

blood pressure reflexes. This difference is also apparent, though less pronounced, in the case of methadon. However, our observations, which are based on a comparison of the values of the regional and systemic reflexes, are insufficiently precise to warrant the assertion that these substances exert a selective influence on the coronary vessels alone.

TABLE 15. EFFECT OF ANALGESICS (MORPHINE, THECODEINE, DEMEROL, METHADON) ON CORONARY VASCULAR REFLEXES AFTER STIMULATION OF THE AFFERENT FIBERS OF THE TIBIAL AND MEDIAN NERVES (MEAN DATA WITH THE STANDARD ERROR)

Agent	Dose in mg/kg	Significance of inhibiting action of the substance[1]	Inhibition of coronary vascular reflexes as percent of original values	Inhibition of blood pressure reflexes as percent of original values
Morphine	1 1	n=7 t=5.62 p<0.002	63 ± 6.2	35 ± 10.7
Thecodeine	1 1	n=6 t=8.09 p=0.001	76 ± 10.2	74 ± 10
Demerol	1 1	n=6 t=5.22 p<0.01	69 ± 6.6	66 ± 2.7
Methadon	1 1	n=5 t=4.03 p<0.02	82 ± 8.1	65 ± 8.6

We should also like to point out that coronary vascular reflexes changed to an equal degree under the influence of the analgesics regardless of the particular reflexogenic zone stimulated.

We mentioned above that the use of large doses of analgesics generally increases the reflexes of the coronary vessels. Presumably, the difference in action of the analgesics in relation to the doses used was one of the reasons for the contradictory views of those who have investigated the problem.

In several experiments with analgesics and other neurotropic agents, we observed a phase quality in their effects on regional reflexes. These effects

[1]The significance of the inhibiting action of the substances on the coronary vascular reflexes was determined from the criterion of the significance of the mean difference.

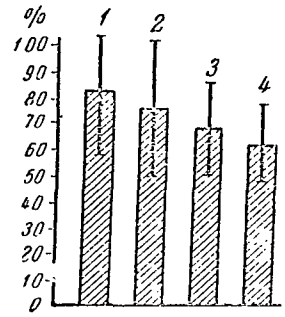

Figure 35. Comparison of the effect of analgesics on coronary vascular reflexes after stimulation of the tibial nerve (the mean values of reflex inhibition are shown in each series of experiments in percentages of the original values with the confidence limits)

1 - methadon; 2 - thecodeine; 3 - demerol; 4 - morphine

were evidently caused not by the specific action of the substances but by the manifestation of certain aspects of their influence on the central nervous system.

In summary, the effectiveness of the analgesics, with the exception of morphine, is not due to their direct influence on the cardiac vessels. Only morphine is capable of increasing the myocardial blood supply as a result of weakened coronary vascular tone. However, when administered in doses equivalent to the therapeutic, these drugs constrict the cardiac vessels. This property combined with their specific pain-relieving action is clearly responsible for the beneficial effect they have on coronary disorders. When used in the clinic, it should also be borne in mind that large doses may promote deterioration of the myocardial blood supply owing to increased coronary vascular tone or intensified coronary reflexes. The only exception is morphine, which in most instances improves the cardiac blood supply.

2. Phenothiazine Derivatives

We previously described a detailed investigation on the effect of phenothiazine derivatives on some factors that determine the cardiac blood supply. According to our observations, chloracizin and mepazine markedly increase the volume rate of the coronary flow, whereas chlorpromazine is very weak in this respect. Despite the capacity of chlorpromazine to reduce the resistance of the cardiac vessels, it has little affect on the rate of blood flow therein because it induces a pronounced hypotension, resulting in lowered effectiveness of hemodynamic regulation of the blood flow in the cardiac vessels.

Judging by the results of clinical trials of these substances, chloracizin, mepazine, and chlorpromazine all have a beneficial effect on coronary disorders. It is thus reasonable to assume that the normalizing influence of the different

phenothiazine compounds on the coronary circulation is due to a variety of mechanisms.

Since coronary vasomotor tone plays a major part in the development of attacks of angina pectoris and this tone can be altered by reflexes, we thought it would be interesting to determine whether there is a connection between the normalizing influence of the phenothiazine derivatives on the cardiac blood supply and their action on the coronary vascular reflexes. It is known from the literature that most of the neuroplegic compounds are capable of inhibiting these reflexes. Chlorpromazine has been the most studied agent in this respect. For example, Courvoisier, Fournel, Ducrot, Kolsky, and Koetschet, (1953) found that a small dose of chlorpromazine (0.1-1 mg/kg) decreased blood pressure reflexes elicited by stimulation of the carotid sinus receptors and that a large dose inhibited them completely. Other investigators confirmed this finding (Dasgupta and Werner, 1954; Krause and Schmidtke-Ruhnau, 1955; Kalkoff, 1955; Medvedev, 1957).

Mepazine is also capable of inhibiting vasomotor reflexes, but to a lesser degree. According to Nieschulz, Popendiker, and Hoffman (1955), mepazine in doses of 3-5 mg/kg decreases blood pressure reflexes elicited by occlusion of the carotid arteries. Yu. I. Vikhlyayev (1958) found that intravenous injection of 5 mg/kg of the drug inhibited blood pressure reflexes from the carotid sinus receptors, afferent fibers of the femoral and sciatic nerves, and intestinal and gallbladder receptors by 20-40 percent of the original values.

There are also published reports describing the inhibiting effect of chlorpromazine and mepazine on blood pressure reflexes elicited by stimulating the mechano- and chemoreceptors of the heart.

Some interesting data were obtained by M. Yu. Ladinskaya (1958), who investigated the effect of chlorpromazine and mepazine on blood pressure reflexes arising in response to restriction of blood circulation in the heart as a result of occlusion of the left descending coronary artery. She found that chlorpromazine has a more powerful effect on the vascular reflexes, whereas mepazine is more capable of normalizing the myocardial blood supply. According to V. V. Zakusov (1960) and I. N. Pidevich (1960), chlorpromazine is also capable of inhibiting the coronary chemoreflex elicited by veratrine or serotonin. The coronary chemoreflex may also be inhibited by other phenothiazine derivatives or by anesthetics potentiated by them (Dews and Graham, 1946; Irmer and Koss, 1953).

There are references in the literature to the fact that the phenothiazine derivatives are capable, as a rule, of inhibiting blood pressure reflexes elicited by stimulating the mechano- and chemoreceptors of various receptor fields. This information is grounds for assuming that these compounds can also inhibit regional vasomotor reflexes.

As in our previous investigations, we elicited coronary vascular reflexes by stimulating carotid sinus receptors and central segments of the tibial and median nerves. The experiments showed that chlorpromazine is the most active of the phenothiazine derivatives. Even in as low a dose as 0.1-0.2 mg/kg it decreased the magnitude of the cardiac reflexes by 40-50 percent of the original

values, its effect after small doses lasting 20-35 minutes. Statistical processing of the results of the experiments with stimulation of the tibial nerve in which chlorpromazine was administered in a dose of 0.3 mg/kg revealed that the coronary vascular reflexes were inhibited by 64 ± 6.7 percent. Judging by the criterion of significance of the mean difference, the inhibiting effect of chlorpromazine on the regional reflexes of the cardiac vessels following administration of a dose of 0.3 mg/kg was significant with a level of $p < 0.02$. Increasing the dose of chlorpromazine to 1 mg/kg generally resulted in total inhibition of the coronary vascular reflexes (fig. 36a), its effect lasting 1-1/2-2 hours. Owing to the particular method that we used, we were unable in most cases to observe the reflexes returning to normal. Changes in the blood pressure reflexes under the influence of chlorpromazine were paralleled by the cardiac reflexes. For example, after administration of a dose of 0.3 mg/kg, these reflexes were inhibited by 73 ± 6 percent.

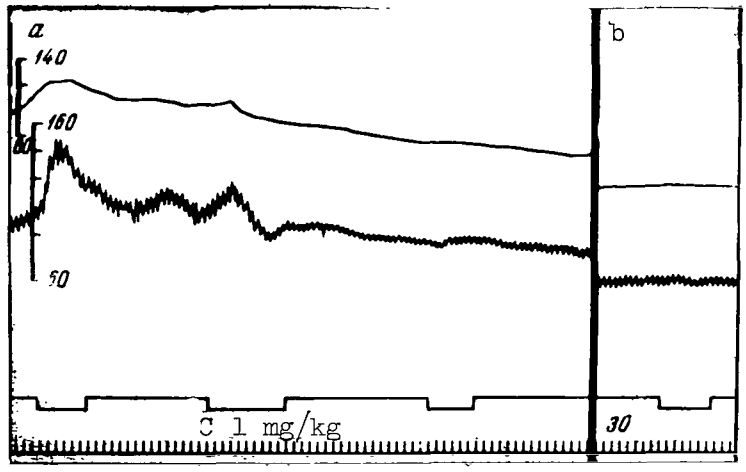

Figure 36a. Effect of chlorpromazine (1 mg/kg) on reflex changes in resistance of the coronary vessels caused by stimulation of the afferent fibers of the tibial nerve. Top to bottom: perfusion pressure, blood pressure, mark of stimulation and injection of the agent, time mark--5 sec.

a--background and injection of chlorpromazine; b--30 min after injection.

Mepazine likewise inhibits the coronary reflexes. Its action, however, is less pronounced and it appears only when administered in doses of 2-5 mg/kg. The inhibiting action of mepazine in a 3 mg/kg dose on the cardiac reflexes is significant with a level of $p < 0.001$.

Statistical processing of the results of the experiments in which mepazine was injected in the aforementioned dose showed that the coronary reflexes

were inhibited by 65 ± 6.6 percent, the effect lasting 25-30 minutes. The blood pressure reflexes were inhibited in the same experiments by 54 ± 5.1 percent.

The least active of the phenothiazine compounds with respect to the vascular reflexes was chloracizin. Its effect was not manifested in all the experiments. The cardiac reflexes were inhibited in most of the experiments (fig. 36b), but in some cases they were completely unaffected (fig. 36c) or even slightly intensified. An increase in the reflexes, amounting to 5-10 percent of the original values, occurred only during the first 5-7 minutes after the drug was administered. This was followed by inhibition of the reflexes.

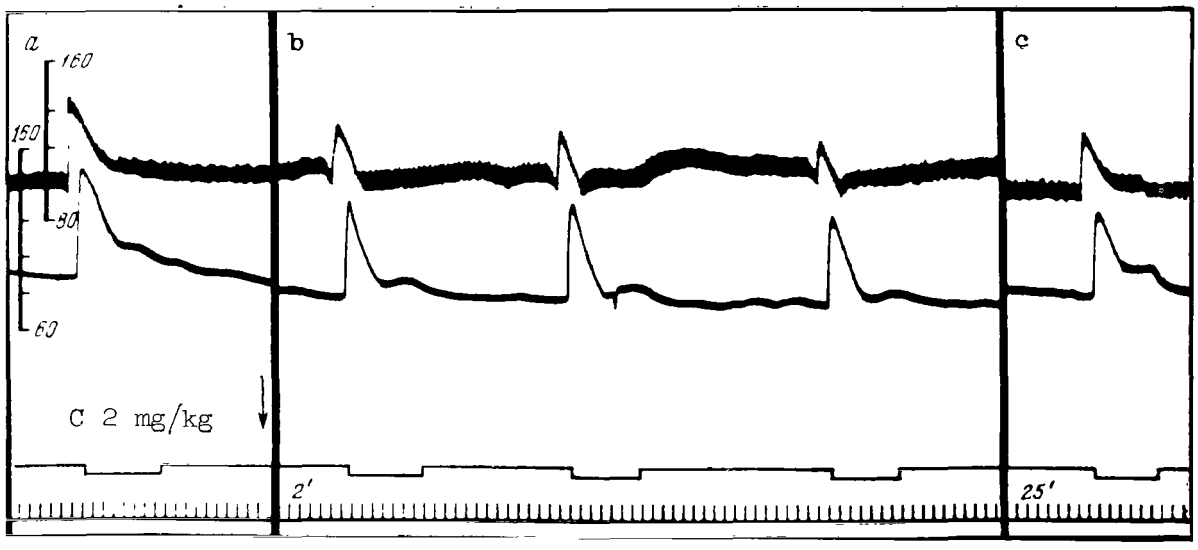

Figure 36b. Decrease in value of coronary reflexes under the influence of chloracizin. Top to bottom: perfusion pressure, blood pressure, mark of stimulation and injection of the agent, time mark--5 sec.

a--background and injection of chloracizin; b-- 2 min after injection; c--25 min after injection.

Statistical processing of the results of the experiments in which chloracizin was used in a dose of 5 mg/kg showed that its effect on the coronary reflexes is an inhibiting one. Judging by the criterion of significance of the mean difference, inhibition of the cardiac reflexes by injection of 5 mg/kg of chloracizin is significant with a level of $p < 0.02$, amounting to an average of 25 ± 7.3 percent in 11 experiments. If in statistical analysis of the experimental data only those experiments are considered in which chloracizin inhibited the coronary reflexes, its effect averaged 47 ± 4.7 percent in 7 experiments (table 16). The blood pressure reflexes changed more stably under the influence of chloracizin than did the cardiac reflexes. After administration of a dose of 5 mg/kg, inhibition of these reflexes

amounted to 40 ± 5.1 percent (all the experiments involving the use of chloracizin in the aforementioned dose were included in the processing). The effect of the drug on the vascular reflexes lasted 20-25 minutes.

Table 16 presents the data reflecting the results of the experiments in which the effect of phenothiazine derivatives on coronary reflexes was investigated. In summary, these substances are capable of inhibiting these reflexes, with chlorpromazine the most active of the compounds under study. The action of mepazine is manifested when it is used in large doses and it is of shorter duration. Chloracizin has an irregular effect on the cardiac reflexes. In the great majority of cases it inhibits them. But in some cases the reflexes do not change or increase for a short period of time.

TABLE 16. EFFECT OF PHENOTHIAZINE DERIVATIVES ON CORONARY VASCULAR REFLEXES AFTER STIMULATION OF THE AFFERENT FIBERS OF THE TIBIAL NERVE.

Agent	Dose in mg/kg	Significance of inhibiting agent of the substances[1]	Inhibition of coronary reflexes as percent of original values[2]	Inhibition of blood pressure reflexes as percent of original values	Remarks
Chlorpromazine	0.3	n=4 t=4.60 p<0.02	64 ±6.7	73 ±6	
	1	n=5 t=6.80 p<0.001	87 ±5.2	89 ±8.2	
Mepazine	3	n=6 t=6.66 p<0.002	65 ±6.6	54 ±9.1	
Chloracizin	5	n=7 t=5.89 p<0.02	25 ±7.3	40 ±5.1	Only the experiments involving the inhibiting action of chloracizin on the reflexes were considered in the statistical processing.
		n=11 t=3.47 p<0.02	47 ±4.7	43 ±7.3	

[1]Significance of the inhibiting action of the substances on the coronary vaccular reflexes was determined from the criterion of the significance of the mean difference.

[2]The table presents the mean data from the experiments in each series with the standard error.

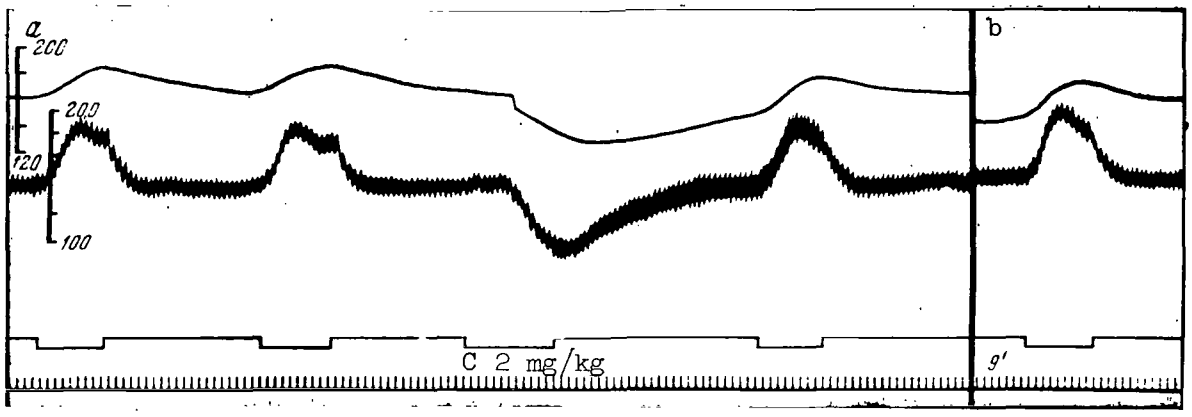

Figure 36c. Absence of change in value of coronary reflexes under the influence of chloracizin (2 mg/kg). Top to bottom: perfusion pressure, blood pressure, mark of stimulation and injection of the agent, time mark--5 sec.

a--background and injection of chloracizin; b--9 min after injection.

The results of our experiments with chlorpromazine and mepazine agree with the data of other investigators who studied the effect of these agents on systemic vasomotor reflexes. However, their mechanism is still obscure. Some relate the inhibiting action of chlorpromazine and, especially, mepazine on vascular reflexes to their anesthetizing the receptors of the vessels (Gadermann and Donat, 1955b; Matthies, Wiegershausen, Otto, and Scholz, 1956; Wiegershausen, Scholz, and Matthies, 1957). But Yu. I. Vikhlyayev (1960) found in experiments with cross circulation in the vessels of the extremities that retained only a nervous connection with the organism that intravenous injection of the donor with 10 mg/kg of chlorpromazine had no perceptible effect on the vascular chemoreceptors, for the latter still remained sensitive to acetylcholine. Thus, endovasal anesthesia does not seem to play an important role in the inhibiting action of neuroplegics on vascular reflexes.

Several authors sought to determine whether this effect is due to the central or peripheral (sympatholytic) action of the drugs. The answer to this question more or less rests on the mechanism of the vasoconstrictor action of chlorpromazine and similar agents. The most convincing data have come from investigators who used the method of cross perfusion of various vascularly isolated parts of the body.

For example, Decourt (1954) perfused with donor blood vessels in the lower trunk of dogs that retained only a nerve connection with the body. Perfusion was carried out by means of a pump that ensured a constant flow of blood. He

found that hypotension developed in the vessels of the isolated region only when chlorpromazine was given to the dog donor. When given to the dog recipient, the vessels of the isolated region constricted while the other vessels in the trunk dilated.

The author cites these experiments as proof that chlorpromazine has no ganglion-blocking action. Some broad conclusions can be drawn from Decourt's investigations.

First, the vasodilator action of the drug does not appear to be connected with its inhibiting action on the central nervous system because the vessels of the isolated region do not dilate after intravenous injection of the recipient with chlorpromazine.

Secondly, the vasoconstrictor action in the isolated region is obviously due to a reflex from the vascular receptors in other regions of the body in response to the lowering of blood pressure there.

Chlorpromazine does not appear to affect the sensitivity of the vascular receptors nor does it suppress central pressor impulses arising from hypotension in the animal's trunk. Similar results were obtained by Kovach, Kleinsorge, Roheim, Iranyi, and Rösner (1957), who studied the mechanism of vasodilator action of mepazine. These investigators found that when donor blood was perfused to the head of a dog recipient that retained its connection with the organism through the spinal cord and vagosympathetic trunks, mepazine intravenously injected into the dog recipient did not change the tone of vessels in the vascularly isolated head. Blood pressure fell in the animal's trunk. It follows from these experiments that peripheral influences predominate in the mechanism of vasodilator action of mepazine.

An analysis of the effect of chlorpromazine on vasomotor reflexes was made by Yu. I. Vikhlyayev (1960), who used in his experiments the method of cross perfusion (with a constant blood flow rate) of vessels of an extremity isolated from the blood circulation but retaining a nerve connection with the organism. The reflexes of these vessels were elicited by stimulating the receptors of the carotid sinus and afferent nerves. Intravenous injection of the cat recipient was found to have no effect on the intensity of the regional reflexes. However, these reflexes were completely inhibited by injecting the donor with the drug or by injecting it directly into the vessels of the isolated extremity.

The observations described above suggest that the peripheral effect of chlorpromazine and mepazine plays a major role in the mechanism of action on the vascular reflexes. Pertinent here are the data of some authors on the central inhibiting action of chlorpromazine with respect to the vascular effects. For example, Dasgupta and Werner (1954) observed that the intracisternal injection of chlorpromazine lowered blood pressure and inhibited reflexes from the carotid sinus. They also found that the drug inhibited pressor responses to stimulation of some regions of the hypothalamus and medulla oblongata. Similar data were obtained by A. V. Val'dman et al. (A. V. Val'dman, Z. N. Ivanova, G. V. Kovalev, V. P. Lebedev and A. I. Shapovalov, 1960). We note, however, that these observations, which are of independent interest, do not warrant definite

conclusions as to the part played by the central component in the mechanism of action of chlorpromazine on the vascular reflexes.

We have already presented data indicating that the efferent link in the reflex arc of the coronary reflexes does not differ in principle from the efferent pathways along which impulses responsible for the development of other reflexes travel. It would seem, therefore, that the prevailing ideas concerning the mechanism of action of the phenothiazine derivatives on vasomotor reflexes are also applicable to the coronary reflexes.

We do not as yet have any experimental data to suggest a possible cause for the inconsistent effect of chloracizin on the cardiovascular reflexes. L. A. Kitayev-Smyk (1960) found that chloracizin in relatively low doses increased the vascular reflexes elicited by electric stimulation of the higher autonomic centers of the brain. Hence, it is reasonable to assume that the inconsistent effects of the drug may stem from the central exciting component in the mechanism of action.

Some clinical implications emerge from a comparison of the activity of the compounds under study with respect to the various indices that reflect the cardiac blood supply. Since the increase in volume rate of the coronary flow under the influence of chlorpromazine is slight, clinical observations on its effectiveness in the treatment of coronary disorders can apparently be attributed to its capacity to inhibit the cardiac reflexes. Elimination of the reflex component does not seem to play an important part in the mechanism of action of chloracizin on the coronary circulation. This view is in line with the clinical data which show that chloracizin is least effective against the neurogenic forms of angina pectoris.

It is clear from our discussion of the phenothiazine derivatives that a knowledge of the mechanism of action of pharmacological agents on the cardiac blood supply is essential for their efficient use in treating various forms of coronary insufficiency.

3. Nitrites and Nitrates

Study of analgesics and phenothiazine derivatives shows that the ability of these agents to affect the magnitude of coronary vascular reflexes is an important link in their mechanism of action on the cardiac blood supply. This is clearly illustrated by the nitrites and nitrates.

Nitroglycerin is one of the oldest drugs used in the treatment of angina pectoris. According to most internists, no other known drug acts so swiftly and safely at the onset of an anginal attack. Its effectiveness is usually related to its vasodilator action which spreads to different vascular regions, especially to the cardiac vessels. However, a review of the literature reveals that this view is based on highly contradictory data. Early in the 20th century it was experimentally demonstrated that nitroglycerin, amyl nitrite, and sodium nitrite relax the smooth muscles of the cardiac vessels (François-Franck, 1903; Schloss, 1913). This finding was later confirmed by a number of investigators who used preparations of the isolated heart in their experiments

(Bodo, 1927; Katz, Linder, Weinstein, Abramson, and Jochim, 1938; Yu. S. Chechulin, 1958, 1960).

On the other hand, the vasodilator effect of nitroglycerin on the cardiac vessels was less pronounced in experiments on intact animals. Only those authors who used the thermoelectric method of recording the blood flow noted a significant acceleration of the volume rate (by 30-100 percent) under the influence of nitroglycerin (Essex, Herrick, Baldes, and Mann, 1936; Essex, Wegria, Herrick, and Mann, 1940; Wegria, Essex, Herrick, and Mann, 1940). Their observations are not wholly convincing because the method does not lend itself to obtaining quantitatively exact data (Dörner, 1954). According to other investigators who recorded the coronary flow by methods permitting more exact calculation of the effect of pharmacological agents throughout a series of experiments, nitroglycerin causes only a slight increase in the volume rate of the coronary flow. For example, Boyer and Green (1941) and Eckenhoff and Hafkenschiel, after recording the volume rate of the coronary flow with bubble and diaphragm flow meters, found that nitroglycerin and sodium nitrite injected intravenously in relatively small amounts caused a slight (7-9 percent) and transient increase in the coronary flow. These substances are much less potent in this respect than papaverine and euphylline. I. Ye. Kisin (1958) investigated the effect of nitroglycerin on blood drainage from the cat coronary sinus and resistance of the coronary vessels under autoperfusion conditions. He found that nitroglycerin injected intravenously (0.1-0.5 mg/kg) or taken per os (1-2 mg/kg) had little effect on drainage from the coronary vessels or on their resistance to the blood flow.

The observations of Gorlin et al. (Smith and Gorlin, 1956; Gorlin, Bozer, and Vester, 1957; Gorlin, Brachfeld, Maelcod, and Bopp, 1959) are of considerable interest. They studied the effect of nitroglycerin on the coronary circulation and on myocardial metabolism in human beings. They found that the drug slightly increased both the volume rate of the coronary flow and the oxygen consumption of the myocardium in healthy persons, but it had no effect on the resistance of the coronary vessels. In patients with angina pectoris, nitroglycerin had no effect whatever on the volume rate of the coronary flow or on myocardial oxygen consumption, but it did reduce the cardiac output, thus lowering arterial and venous pressure and decreasing cardiac activity. The authors concluded that its clinical effectiveness is due not to its capacity to dilate the coronary vessels but mainly to the fact that it reduces cardiac activity and thereby decreases the expenditure of energy required for myocardial contractions. This view is also based on a series of observations on the capacity of nitroglycerin to prevent adrenergic influences on the heart, as reflected in the increased force of myocardial contractions and greater intensity of the metabolitic processes.

The theory underlying these investigations was developed by Raab (1959), who maintains that anginal attacks are the result of the accumulation of catecholamines in the myocardium which intensify oxygen consumption and promote hypoxia. Raab and coworkers (Raab and Humphreys, 1947; Raab and Lepeschkin, 1950a, 1950b) also assume that the mechanism of action of some pharmacological agents effective in treating angina pectoris may be due to their antiadrenergic action. Investigating nitroglycerin from this standpoint, they found that it decreased the EKG changes (inversion of the T wave) caused by

administering epinephrine and norepinephrine. Later, Eckstein, Newberry, McEachern, and Smith (1951) made a more detailed study of the action of nitroglycerin on some of the effects produced in the myocardium by stimulating the sympathetic nervous system. In experiments on dogs, they recorded the coronary flow, myocardial oxygen consumption, forces of cardiac contractions, and electrocardiogram under normal conditions and after stimulation of the sympathetic nervous system (by an electric current or by injection of epinephrine). They found that even large doses of nitroglycerin did not diminish the intensity of the metabolitic processes in the myocardium or other effects augmented by stimulation of the sympathetic nervous system and thus lacking in antiadrenergic action. The authors are critical of Raab for basing his argument about the antiadrenergic action of nitroglycerin on EKG observations. However, the inversion of the T wave caused by the catecholamines and regarded by Raab as an indicator of myocardial hypoxia does not develop even after prolonged impairment of the cardiac blood supply resulting from occlusion of one of the coronary arteries, i.e., under the conditions of sharp myocardial hypoxia.

Eckstein's data were later confirmed by Popovich and Roberts (1956), who found that nitroglycerin did not lower the level of the metabolitic processes of the myocardium whose intensity was increased by norepinephrine. Yet, according to Darby et al. (Darby, Sprouse, and Walton, 1958; Darby and Aldiner, 1960), nitroglycerin possesses an inotropic action, which appears after the development of hypotension. This effect does not occur after a sympathectomy, but it is more pronounced when the sympathetic nervous system is stimulated. In the opinion of these investigators, the decrease in effort exerted by the heart (after the use of nitroglycerin) to overcome the sympathetic stimulation of the myocardium plays a major role in the drug's mechanism of action in angina pectoris.

There is also the view that nitroglycerin owes its effectiveness against coronary circulatory disorders to its capacity to stimulate the development of collateral vessels. For example, Smith (1921) found in experiments on dogs with impaired coronary circulation caused by ligation of a coronary artery that injection of nitroglycerin in the region of an infarct caused cyanosis to disappear because of the small collateral vessels opening up. According to Zoll and Norman (1952), nitroglycerin promotes the development of interarterial anastomoses in guinea pigs after the coronary vessels have been constricted. It will be noted, however, that these properties are less pronounced in nitroglycerin than in some other substances capable of dilating the coronary vessels. A. A. Myazdrikova (1960), who compared nitroglycerin, papaverine, and chloracizin with respect to their influence on the development of collateral circulation in the myocardium after experimental infarction, found nitroglycerin to be the least potent of all.

In summary, there are now two views prevalent concerning the mechanism of the normalizing action of nitroglycerin on the coronary circulation. The older and more established one is that nitroglycerin can dilate the cardiac vessels and thus improve the blood supply. This view is not completely convincing because the drug's clinical effectiveness can scarcely be due solely to its capacity to slightly increase the volume rate of the coronary flow. The other view ascribes the drug's effectiveness to its antiadrenergic action, but most investigations have failed to confirm it. It is also doubtful because it is

based on the conception of Raab (1959), who regards the complex and multifaceted syndrome of angina pectoris solely as the result of catecholamines accumulating in the myocardium.

As already noted, the experimental observations advanced by the author in favor of his view do not exclude the possibility of other factors being involved in the development of acute coronary insufficiency. Thus, despite the long clinical use of nitroglycerin, the underlying mechanism responsible for its effectiveness in relieving anginal attacks remains obscure.

One peculiarity of nitroglycerin is worth noting. Unlike most of the pharmacological agents used in the treatment and prevention of coronary insufficiency, nitroglycerin is usually effective as soon as it is taken. This being the case, it occurred to us that such rapid action might well be due to its effect on reflexes spreading to the cardiac vessels and causing them to become constricted.

We presented above many factors showing that reflexes of this kind may play an important part in the onset of anginal attacks. Before investigating this aspect, we thought it necessary to make a quantitative evaluation of the effect of nitroglycerin on the volume rate of the coronary flow and on the resistance of the cardiac vessels because of the pertinence of such information in elucidating the role of the drug's direct action on the coronary vessels in realizing its effect on the cardiac blood supply.

To determine whether these particular properties of nitroglycerin are unique or are also present in other drugs of the same group, we performed a parallel series of experiments with sodium nitrite. Both compounds were injected intravenously. Nitroglycerin in doses of 0.1-0.5 mg/kg produced rather distinct changes in the coronary circulation without markedly affecting the general hemodynamics of the organism. On the basis of the same criteria, we used 0.5-1 mg/kg doses of sodium nitrite. In some control experiments nitroglycerin was administered per os at the rate of 1-2 mg/kg.

We were led to perform experiments of this kind by observations on the capacity of nitroglycerin to influence the cardiac vessels by reflexes from the buccal mucosa (V. N. Solov'yev). Our experiments, however, showed that the volume rate of the coronary flow changes to about the same extent regardless of which method is used, whether nitroglycerin is injected intravenously in doses of 0.5-1 mg/kg or is taken per os in doses of 1-2 mg/kg. The only difference is the time the attack sets in.

Since nitroglycerin was used in an alcohol solution, control experiments were also run with the injection of alcohol in the appropriate concentration. No significant differences were noted in the condition of the coronary circulation.

In the first series of experiments, we investigated the effect of nitroglycerin and sodium nitrite on the volume rate of the coronary flow (table 17). Nitroglycerin injected intravenously in a dose of 0.5 mg/kg increased the rate slightly. In 11 experiments, the increase in outflow from the coronary sinus averaged 18 ± 2.6 percent while blood pressure dropped 16 ± 2 percent. The

effect was brief and both indices usually returned to their original level in 5-6 minutes.

TABLE 17. EFFECT OF NITROGLYCERIN AND SODIUM NITRITE ON THE VOLUME RATE OF THE CORONARY FLOW, RESISTANCE OF THE CORONARY VESSELS, AND BLOOD PRESSURE (MEAN DATA IN PERCENT OF ORIGINAL LEVEL WITH THE STANDARD ERROR)

Agent	Dose in mg/kg	Changes in volume rate of coronary flow	Confidence limits	Changes in resistance of coronary vessels	Confidence limits	Changes in blood pressure	Confidence limits
Nitroglycerin . . .	0,5	+18±2,6	+11,8÷+24,2	— 7±1,4	—2,3÷—11,7	—16±2,5	—10,7÷—21,3
Sodium nitrite . . .	1	+17±5,2	+ 5,7÷+28,3	— 10±2,6	—3,7÷—16,3	—19±3,	—12,6÷—25,4

The results of the experiments with sodium nitrite were substantially the same. In 12 experiments, a dose of 1 mg/kg caused the volume rate of drainage from the coronary sinus to increase by 17 ± 5.2 percent on the average while blood pressure dropped 19 ± 3 percent. Thus, the two drugs are alike in intensity of effect on the volume rate of the blood flow, but the dynamics of the development of the effect is different. Nitroglycerin clearly lowers blood pressure as soon as it is administered. The volume rate of the blood flow either remains unchanged or decreases slightly. After 1 or 2 minutes it increases. This effect is transient and the volume rate of blood outflow returns to the initial level in 6-8 minutes.

Unlike nitroglycerin, sodium nitrite causes the volume rate of the coronary flow to increase gradually until it reaches a peak 3 or 4 minutes after administration. At the same time blood pressure is dropping. Sodium nitrite has a more sustained effect than nitroglycerin. The volume rate of the coronary flow returns to the initial level 14-15 minutes after administration (fig. 37).

In a second series of experiments, we investigated the effect of the two drugs on resistance of the coronary vessels. Nitroglycerin in a dose of 0.5 mg/kg was found to cause slight changes in resistance. Statistical processing of the results showed that in 15 experiments, nitroglycerin reduced resistance only by 7 ± 1.4 percent on the average. In some experiments there was either no change or a slight increase (fig. 38). Like nitroglycerin, sodium nitrite slightly decreased the resistance of the cardiac vessels. In 7 experiments,

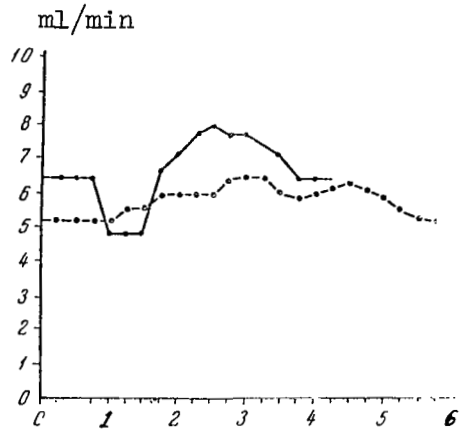

Figure 37. Effect of nitroglycerin and sodium nitrite on the volume rate of the coronary flow. Ordinate - volume rate of the coronary flow in ml/min. Abscissa - time in minutes. Solid line - changes in blood flow under the influence of nitroglycerin (0.5 mg/kg), broken line - changes in blood flow under the influence of sodium nitrite (1 mg/kg).

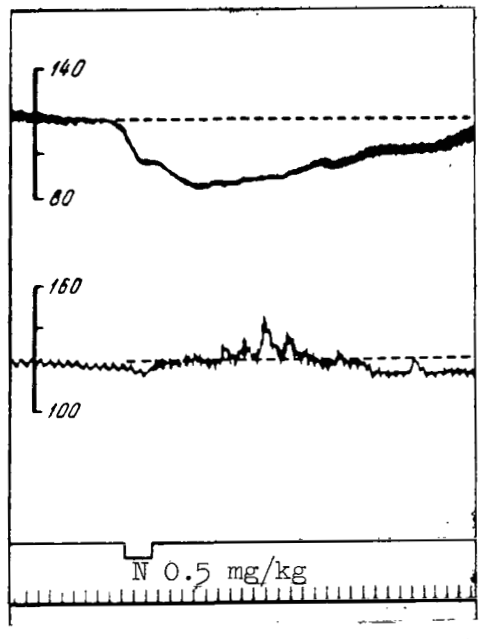

Figure 38. Effect of nitroglycerin (0.5 mg/kg) on resistance of the coronary vessels and on blood pressure. Top to bottom: blood pressure, perfusion pressure, mark of administration of the drug, time mark - 5 seconds. Broken lines - original level of blood and perfusion pressures.

the resistance of the coronary vessels after intravenous injection of the drug in a dose of 1 mg/kg decreased by 10 ± 2.6 percent on the average. As in the experiments with recording of blood drainage, blood pressure changed more gradually after the action of sodium nitrite than after nitroglycerin. The results of statistical processing of this series of experiments are presented in table 17.

Our observations indicate that nitroglycerin and sodium nitrite have only a slight effect on the volume rate of the coronary blood flow and resistance of the coronary vessels. This suggests the desirability of reviewing the earlier opinion on nitroglycerin as a drug capable of selectively dilating the coronary vessels. Of interest are the results of the series of experiments in which we investigated the effect of nitroglycerin on the resistance of vessels in different parts of the body (heart, extremities, small intestine). We found that it rather sharply reduced the resistance of the intestinal vessels while scarcely affecting that of the coronary vessels. Presumably, the hypotensive effect of nitroglycerin is realized mainly through dilatation of the blood vessels in the abdominal cavity.

To determine whether the increase in coronary blood flow produced by nitroglycerin is responsible for its clinical effectiveness, we compared the intensity of its action with that of papaverine, tiphen (2 - diethylaminoethyl diphenylacetate hydrochloride), and phenothiazine derivatives (chloracizin, mepazine, and chlorpromazine). We plotted the graph in the section on "Chloracizin" (p. 102, fig. 30). It is noteworthy that nitroglycerin is one ourth as potent as papaverine. Yet nitroglycerin is more effective than papaverine in the treatment of angina pectoris. This suggests that its effectiveness as an agent for normalizing the coronary circulation is not due solely to its vasodilator action on the coronary vessels. However, it was reasonable to assume that it is more effective in pathological states, when the cardiac vessels are changed by atherosclerosis or are in spasm. To prove this, we ran a series of chronic experiments on cats in which pituitrin was used to induce spasm of the coronary vessels. The design of the experiments was as follows. Three days before the main experiment involving administration of the drugs, we performed a control experiment to record EKG changes after intravenous injection of pituitrin (2 U/kg). Then at 3-day intervals experiments were run in which pituitrin was injected after the administration of nitroglycerin (0.5 mg/kg), chloracizin (5 mg/kg), and papaverine (2 mg/kg). The series of experiments ended with the injection of pituitrin alone. A total of 10 animals was used. The agents under study were infused intravenously 2-3 minutes before the injection of pituitrin.

In summary, a comparison of the effectiveness of chloracizin, papaverine, and nitroglycerin led to the same conclusion as that drawn from investigations of their effect on the cardiac blood supply both under normal conditions and after a pituitrin-induced spasm of the cardiac vessels. Chloracizin proved to be the most effective, for it completely eliminated the EKG changes that set in after the myocardial blood supply was impaired. Papaverine was also effective in most experiments in that it prevented arrhythmia and tended to level out the EKG changes reflected in alteration of the T wave and position of the S-T segment. Nitroglycerin had no significant influence on the myocardial blood supply when the coronary vessels were in spasm induced by

pituitrin. In just a few experiments it slightly reduced the impairment of the cardiac rhythm caused by an insufficient blood supply.

The results of one of the experiments performed to compare the effect of the above-mentioned substances on EKG changes induced by pituitrin are presented in figure 39.

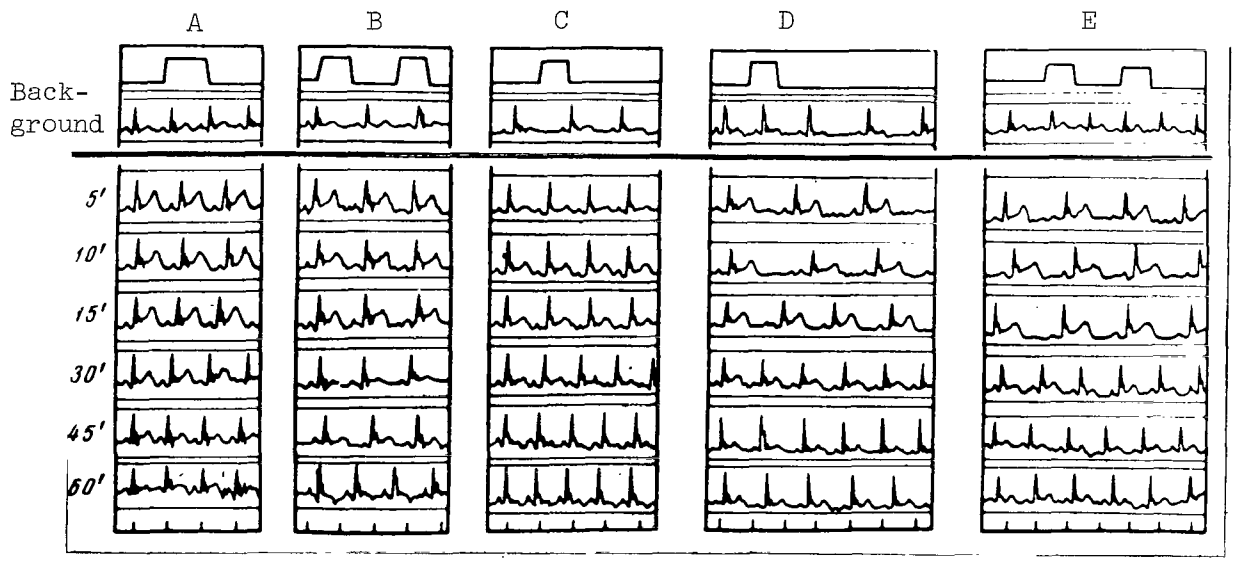

Figure 39. Comparison of the prophylactic effect of nitroglycerin, chloracizin, and papaverine after impairment of the cardiac supply by intravenous injection of pituitrin

A - EKG changes induced by intravenous injection of pituitrin (2 U/kg); B - EKG changes induced by pituitrin after administration of nitroglycerin (0.5 mg/kg); C - EKG changes induced by pituitrin after administration of chloracizin (5 mg/kg); D - EKG changes induced by pituitrin after administration of papaverine (2 mg/kg). All the pharmacological agents were injected intravenously 2 minutes before the injection of pituitrin; E - control experiment with only pituitrin injected.

Thus, after experimental impairment of the coronary circulation by pituitrin, which is known to possess a direct vasoconstrictor action (by contracting the smooth muscles of the arterioles), nitroglycerin is as inactive as under normal conditions. According to the observations of G. A. Markova (1960), nitroglycerin has a weak effect on the volume rate of the coronary flow in experimental myocardial infarction.

A study of the action of nitroglycerin on the coronary circulation with the coronary vessels in spasm convinced us once again that the effectiveness of the drug in relieving anginal attacks is not to be ascribed solely to its

capacity to dilate the cardiac vessels. Accordingly, the objective of our next series of experiments was to study the effect of nitroglycerin on coronary vascular reflexes.

The experiments showed that in doses as low as 0.1-025 mg/kg, nitroglycerin significantly (30-40 percent above the original values) inhibited the coronary reflexes after all the reflexogenic zones under study were stimulated. Increasing the dose to 0.3-0.5 mg/kg sometimes inhibited the reflexes entirely.

The results of statistically processing the experiments with nitroglycerin and sodium nitrite are presented in table 18. Since the intensity of a reflex from the carotid sinus receptors varies with the level of arterial pressure, which is lowered by nitrites, only the changes in the reflexes caused by stimulation of the nerves were considered in quantitative determination of their intensity. It appeared that the level of significance of the inhibiting action of nitroglycerin on the coronary vascular reflexes was very high ($p < 0.001$).

TABLE 18. EFFECT OF NITROGLYCERIN AND SODIUM NITRITE ON CORONARY VASCULAR REFLEXES AFTER STIMULATION OF AFFERENT FIBERS OF THE TIBIAL NERVE (MEAN DATA IN PERCENT OF THE ORIGINAL LEVEL WITH THE STANDARD ERROR)

Agent	Dose in mg/kg	Significance of inhibiting action of the substances[1]	Inhibition of coronary vascular reflexes in percent of original values	Inhibition of blood pressure reflexes in percent of original values
Nitroglycerin	0.5	n = 12 p < 0.001 t = 6.25	66 ± 8.7	42 ± 4
Sodium nitrite	1	n = 5 p < 0.01 t = 6.24	74 ± 14.4	53 ± 15.8

In a dose of 0.5 mg/kg nitroglycerin inhibited the cardiovascular reflexes arising from stimulation of afferent fibers of the tibial and median nerves by 66 ± 8.7 percent (mean data of 12 experiments). The effect lasted 15-18 minutes. Blood pressure reflexes in the same experiments were inhibited by 42 ± 4 percent of the original level. It is interesting to note that in many of the experiments nitroglycerin had a rather marked effect on the regional reflexes. Despite complete inhibition of the cardiovascular reflexes, the intensity of the blood pressure reflexes decreased only by 30-50 percent of the original level (fig. 40).

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[1]The significance of inhibition of coronary vascular reflexes was determined from the criterion of significance of the mean difference.

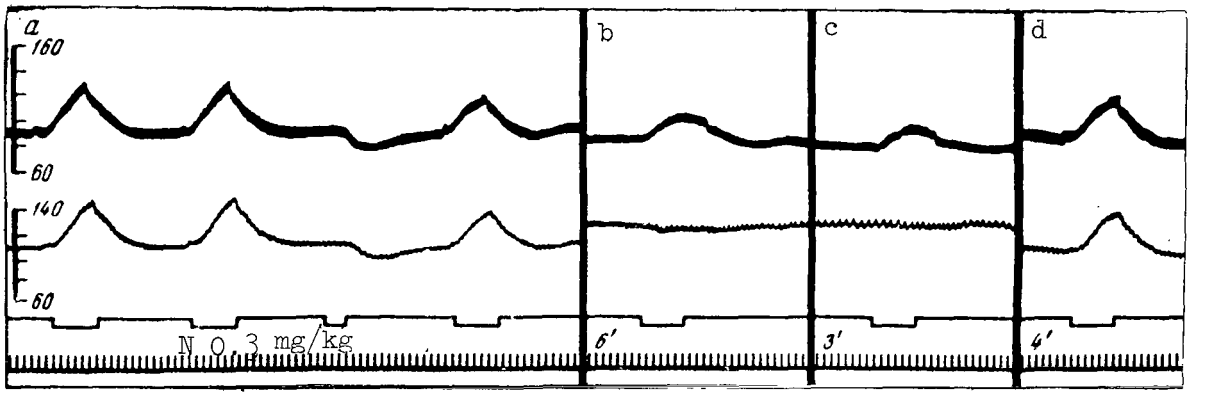

Figure 40. Effect of nitroglycerin (0.5 mg/kg) on coronary vascular reflexes elicited by stimulating afferent fibers of the tibial nerve. Top to bottom: blood pressure, perfusion pressure, mark of stimulation and administration of the agent, time mark - 5 seconds.

a - background and administration of nitroglycerin; b - 6 minutes after administration; c - 9 minutes after administration - complete inhibition of cardiovascular reflexes; d - 13 minutes after administration - restoration of reflexes to the original level.

The administration of nitroglycerin per os (1-2 mg/kg), as in the experiments when it was injected intravenously, resulted in inhibition of the coronary vascular reflexes, although the condition of the vessels themselves was not perceptibly affected.

Like nitroglycerin, sodium nitrite inhibited the cardiovascular reflexes. The coronary vascular reflexes were inhibited even by low doses (0.3-0.5 mg/kg). However, its effect was most pronounced when administered in a dose of 1 mg/kg. The inhibition of cardiovascular reflexes by sodium nitrite after stimulation of afferent fibers of somatic nerves was statistically significant ($p < 0.05$). When injected intravenously, nitroglycerin in a dose of 1 mg/kg inhibited these reflexes 74 ± 14.4 percent (mean data of 5 experiments). Blood pressure reflexes were also inhibited by the drug. In the same experiments, inhibition of the blood pressure reflexes amounted to 53 ± 15.8 percent (table 18). Unlike nitroglycerin, the effect of sodium nitrite on reflex changes of perfusion and blood pressure became manifested slowly, but it was more persistent. The reflexes did not return to the original level until 30-35 minutes after administration of the substances.

Thus, our experiments demonstrate that nitroglycerin and sodium nitrite inhibit reflexes of the cardiac vessels without significantly dilating them.

Of considerable interest is the mechanism underlying the inhibiting action of the nitrites on the vascular reflexes in general and the cardiovascular reflexes in particular. We started experiments to elucidate the matter by investigating the effect of nitroglycerin on the conduction of excitation in the efferent part of the reflex arc. Since coronary vascular reflexes are executed by means of conduction through the sympathetic ganglia, we performed experiments in which we recorded biocurrents of the inferior cardiac nerves after electric stimulation of their preganglionic fibers at the level of the 3rd-4th thoracic sympathetic ganglion by superintense rectangular stimuli at a frequency of 30 per second lasting 0.5 second. The biocurrents were derived from the inferior cardiac nerve by means of a bipolar platinum electrode. The experiments showed that even in large doses (0.7-1 mg/kg) nitroglycerin does not affect the transmission of excitation in the sympathetic ganglia. The results of one of these experiments are presented in figure 41.

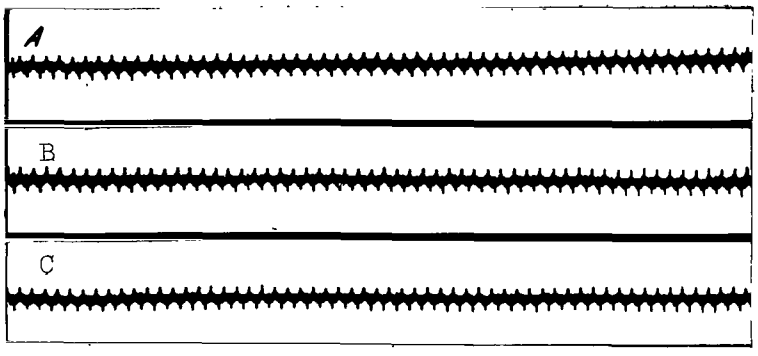

Figure 41. Absence of effect of nitroglycerin on the transmission of excitation in the thoracic sympathetic ganglion.

A - biocurrents of inferior cardiac nerve after stimulation of its preganglionic fibers; B - after administration of nitroglycerin in a dose of 0.5 mg/kg; C - after administration of nitroglycerin in a dose of 1 mg/kg.

The question then arose of whether nitroglycerin is capable of blocking the conduction of excitation from the postganglionic fibers to the vessels. We encountered considerable difficulty in designing appropriate experiments because when the sympathetic nerves supplying the heart are stimulated, it is impossible to distinguish between the vascular effects and the extravascular influences elicited by sympathetic stimulation of the myocardium. To determine whether the inhibiting effect of nitroglycerin on vascular reflexes may be due to peripheral (sympatholytic) or central action, we performed experiments in which we used as a model reflexes of the small intestine elicited by electric stimulation of the tibial nerve. The experiments were conducted under the conditions of cross blood circulation. The small intestinal vessels of the cat recipient were carefully isolated from the general circulation and perfused through a perfusion pump (at a constant flow rate) with the blood

of the cat donor. The small intestine of the cat recipient was connected to the organism only through the nerves (fig. 42a). Electric stimulation of afferent fibers of the tibial nerve (60 cps, 5 msec, 10 v) caused reflex constriction of the vessels of the small intestine. Intravenous injection of the donor with nitroglycerin or the vessels of the region being perfused resulted in their dilating. Meanwhile, however, the intensity of the reflex did not change. On the other hand, when nitroglycerin (0.5 mg/kg) was injected intravenously into the cat recipient, the reflexes decreased considerably or were completely inhibited, the effect lasting 17-20 minutes (fig. 42b). We concluded from these experiments that the inhibiting effect of nitroglycerin on the vascular reflexes is due not to its peripheral action but to its influence on the central nervous system.

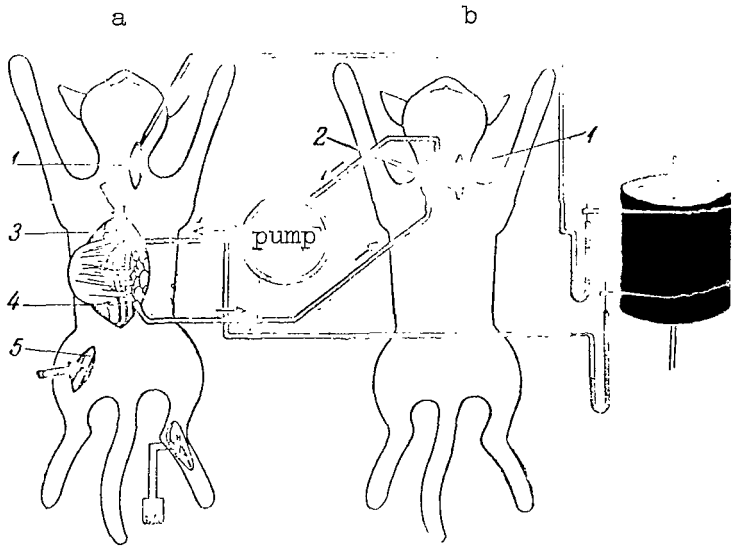

Figure 42a. Experiment with perfusion of donor blood into small intestine vessels retaining only a nerve connection with the organism. The light arrows show the path of the blood from the donor's carotid artery through the perfusion pump system to the recipient's intestinal vessels and then through the venous system of the recipient's small intestine to the donor's jugular vein. The heavy arrows indicate the three methods of administering glycerin used in the experiments.

a - recipient; b - donor; 1 - carotid artery; 2 - jugular veins; 3 - superior mesenteric artery; 4 - superior mesenteric vein; 5 - femoral vein.

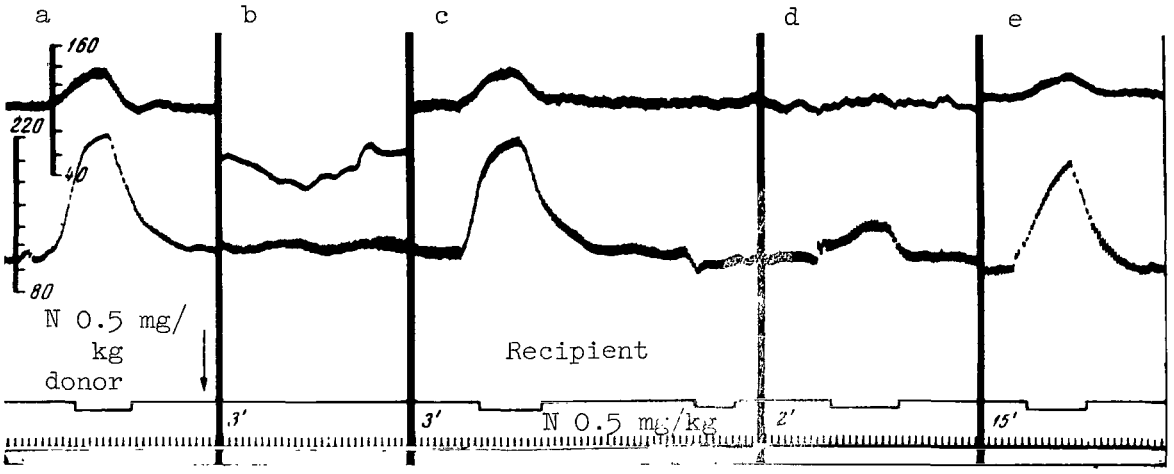

Figure 42b. Effect of nitroglycerin on reflex changes in resistance of small intestinal blood vessels under the conditions of cross perfusion.

Top to bottom: perfusion pressure, blood pressure, mark of administration of the agent, time mark - 5 seconds

a, b - background and reaction of small intestinal vessels to injection of nitroglycerin (0.5 mg/kg) into the donor; b - absence of changes in intensity of reflex with this method of administration; c - immediately after intravenous injection of nitroglycerin (0.5 mg/kg) into the recipient - inhibition of intestinal vascular reflexes; e - restoration of reflexes to the original level.

To find out whether these conclusions held true for the coronary vascular reflexes as well, we ran still another series of experiments in which nitroglycerin was injected directly into the cerebral vessels through the vertebral artery so as to delay its reaching the cardiac vessels. Accordingly, the size of the perfusion system was artificially enlarged with a coil attached to the pump. The diameter and number of spirals were selected in such a fashion that the time required for the blood to flow from the carotid artery to the coronary vessels would take 2 minutes longer. The temperature of the blood passing through the coil was maintained by means of a water bath and thermoregulator (fig. 43a).

It was found that nitrogen injected into the vertebral artery inhibited the coronary vascular reflexes within 30-35 seconds, although it did not reach the coronary vessels for 2 minutes. Note that the reflexes were inhibited by doses as low as 0.03 mg/kg and distinctly so by doses of 0.09-0.1 mg/kg (fig. 43b).

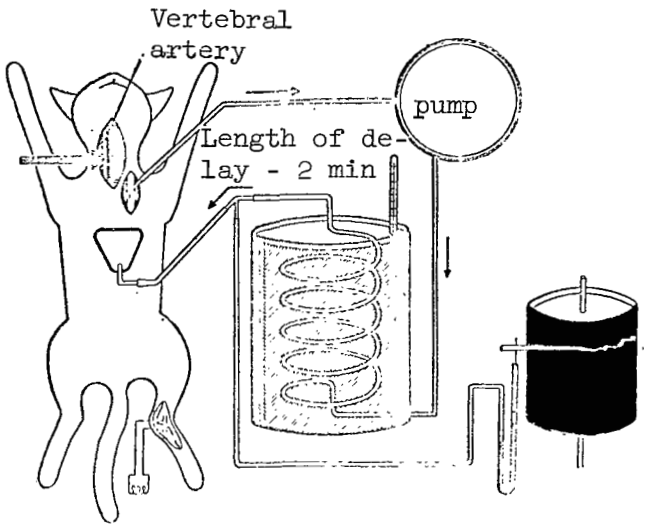

Figure 43a. Diagram of experiments with nitroglycerin delayed in reaching the cardiac vessels. The light arrows show the path of the blood from the cat carotid artery through the perfusion pump system to the outlet of which is connected a coil. The heavy arrow indicates the introduction of nitroglycerin into the cerebral vessels through the vertebral artery.

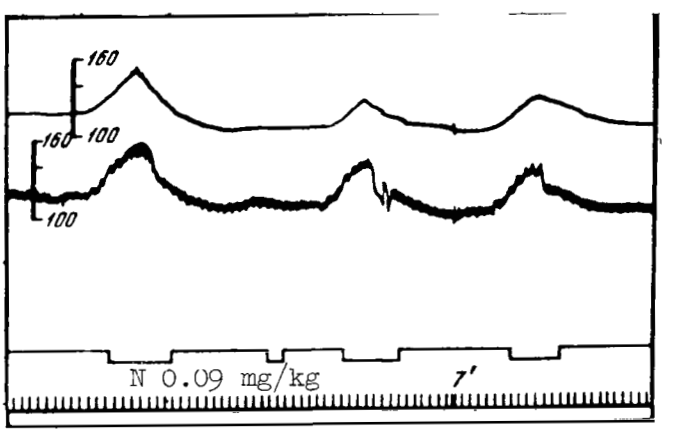

Figure 43b. Effect of nitroglycerin (0.09 mg/kg) injected into cerebral vessels on reflex changes in resistance of the coronary vessels and on blood pressure. Top to bottom: perfusion pressure (resistogram), blood pressure, mark of stimulation and administration of the agent, time mark - 5 seconds.

These experiments showed that the inhibiting action of nitroglycerin on coronary vascular reflexes is due to its influence on the central nervous system.

We do not as yet have experimental data that might throw light on the level at which the central action of nitroglycerin is realized or on the reasons for the somewhat selective action exhibited in our experiments by glycerin on the coronary vascular reflexes. These problems cannot be solved without the use of special techniques.

Our observations which showed that nitroglycerin inhibits coronary vascular reflexes without markedly dilating the vessels warrant a reexamination of earlier ideas on the nature of its effect on the coronary circulation. The effectiveness of the drug in angina pectoris obviously cannot be attributed purely to its direct vasodilator action, as was previously thought. Its capacity to inhibit the reflexes that result in constriction of the coronary vessels may well play a major role in its mechanism of action on the cardiac blood supply.

As for the nitrites and nitrates, this group seems to contain unusually promising drugs for treating angina pectoris, judging by observations of recent years, especially some new ones which have a longer lasting action than nitroglycerin. Among the drugs now solidly entrenched in medical practice are nitranol (triethanolamine trinitrate diphosphate) and nitropeptone (pentaerythritol tetranitrate). Note, however, that they have been scarcely investigated experimentally. Their pharmacological action has been studied mainly with respect to the duration of the vasodilator effect as compared with that of the more familiar drugs.

Both drugs have been demonstrated to possess the capacity to intensify blood drainage from the coronary vessels in experiments on the isolated heart and to increase the volume rate of the coronary flow in intact animals (Melville and Lu, 1951; Winsor and Scott, 1955; M. D. Mashkovskiy and B. A. Medvedev, 1958). It is interesting to note, however, that Winsor and Scott, who recorded the blood flow in the coronary vessels with a rotameter, were able to increase the rate of the blood flow with nitropeptone in doses equivalent to the therapeutic by only 9 ± 4 percent (mean data of 4 experiments).

These findings imply that the effectiveness of nitropeptone in the treatment of angina pectoris can scarcely be attributed to its direct vasodilator effect. This view is indirectly confirmed by the fact that both of the above-mentioned drugs do not change the level of systemic arterial pressure and that they seem to affect the blood circulation in different vascular regions of the body unequally. For example, according to Winsor and Scott, nitropeptone scarcely affects the skin temperature and flow of blood in the fingers (plethysmographic study). Pfeiffer (1950) investigating the effect of nitranol on several hemodynamic indices in human beings found that it reduces the cardiac output and activity without lowering blood pressure. Calculation of the total peripheral resistance showed that it rises only slightly. These data can be explained by the fact that nitranol, like nitropeptone, affects the resistance of blood vessels in different parts of the body unequally.

The above-described properties are grounds for believing that the mechanism of action of the substances on the coronary circulation, like that of nitroglycerin, is not due solely to their direct myotropic effect on the cardiac vessels. Special experiments are needed to throw more light on the subject.

Nitranol and nitropeptone have been extensively tested in the clinic, if not experimentally studied. It has been found that when taken orally, their effect sets in slowly, reaching a maximum the first hour but persisting for 4-5 hours more. They are also used to prevent anginal attacks (Spuhler, 1949; Dailhei-Geoffrey, 1951; Palmer and Ramsey, 1951; Winsor and Humphreys, 1952; Weitzman, 1953; Heller, 1956; Fuller and Kassel, 1955; Risman, Aetman, and Koretsky, 1958, A. B. Zborovskiy, 1957; Z. V. Osipova, 1958; I. A. Levina and Ye. A. Gruzina, 1958; M. D. Zaukin, N. P. Gorokhova, Z. A. Stefadu, T. A. Zaikina, and V. O. Moiseyev, 1959; A. M. Yeliseyeva, G. A. Serova, and T. B. Lirina, 1959; others).

Judging from the results of a comparative EKG study of the effectiveness of these drugs in the treatment of angina pectoris, nitropeptone is the more active. This was the conclusion, for example, of Russek, Zohman, Drumm, Weingarten, and Dorset (1955), who compared their action with that of other coronary dilators with prolonged action - nitranol (metamine, paveril, and nitroglycerin) EKG changes in patients after they performed standard exercises served as the test. They found that only nitropeptone is capable of eliminating the EKG changes indicative of an impaired cardiac blood supply. The other substances tested do not have this action and they produce only a subjective improvement in patient's condition. It is interesting to note that the capacity to improve the EKG changes attendant upon physical exertion by patients with angina pectoris is characteristic of very few of the pharmacological agents used for coronary insufficiency. Only nitroglycerin and papaverine in large doses above the usual therapeutic ones have it (Russek, Urbach, Doerner, and Zohman, 1953). Thus, this property, which is found mainly in the nitrites, evidently reflects in part the nature of their mechanism of action.

In summary, the following conclusion may be drawn from our observations on the effect exerted by pharmacological agents on coronary vascular reflexes. Analgesics - morphine, thecodeine, demerol, and methadon - in relatively small doses (1-2 mg/kg) can inhibit these reflexes. Methadon is particularly active in this respect, for in most cases it inhibits them completely. The phenothiazine derivatives have a potent effect on the cardiovascular reflexes. Even in such small doses as 0.5-1 mg/kg chlorpromazine can inhibit these reflexes significantly, although chloracizin has a much weaker effect, even when doses 10 times as large (5 mg/kg) are used. The inhibition of coronary vascular reflexes apparently plays a major role in the nitrites' mechanism of action on the cardiac blood supply.

Thus, our investigations have shown that studies dealing with the effect of various drugs on nervous regulation of the cardiac vessels may well provide fresh insight into their mechanism of action on the cardiac blood supply.

In summary, we wish to emphasize once again that pharmacology now has broad opportunities for aiding practicing physicians in controlling coronary disease. However, the present level of research is not sufficiently developed to permit the use of all conceivable ways by which drugs can act on the cardiac blood supply. Until recently, information on agents capable of improving the cardiac circulation was limited mostly to substances that relax the smooth muscles in the walls of the coronary vessels. This gave rise to the term "vasodilators", which have frequently been erroneously equated with substances that improve the

coronary circulation. But we can now say with some confidence that dilatation of the coronary vessels is not the only way of normalizing the cardiac blood supply. It is often necessary to use drugs that normalize the coronary circulation by relieving spasms provoked by reflex vasoconstrictor influences. These drugs are clearly just as necessary to halt acute attacks of angina pectoris as agents of myotropic action, which dilate the coronary vessels and help to accelerate the development of collateral circulation in the heart whose vessels have been affected by chronic atherosclerosis.

While papaverine, the purines (theobromine, theophylline, and euphylline), and chloracizin are effective in cases of chronic coronary insufficiency, the nitrites or analgesics are generally active in acute attacks of angina pectoris. Elimination of neurogenic influences on the coronary vessels may be also achieved by using neuroplegic agents (chlorpromazine, mepazine).

Action on myocardial metabolism is extremely important in normalizing the cardiac blood supply. Recent studies indicate that a number of pharmacological agents previously regarded as possessing myotropic action improve the coronary circulation by acting primarily on myocardial metabolism. There are grounds for believing that papaverine, for example, has such a mechanism of action on the cardiac blood supply.

It is to be hoped that further research on the pharmacology of the coronary circulation will not only enlarge the arsenal of pharmacological agents available to the internist, but help him to use them more efficiently in treating various circulatory disorders.

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